Placebo, nocebo and contextual factors:

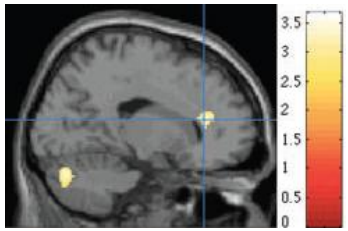
history, research and clinical practice

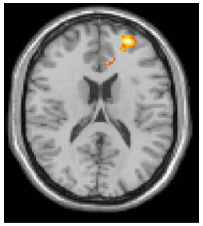
PLACEBO in modern science: 3 contexts

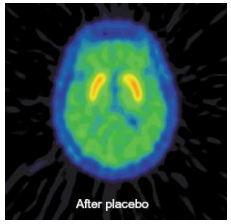
- **In clinical trials → the aim is to REDUCE the placebo effect**

Scientific research =/ Clinical trials-> In clinical trials the aim is not to understand how the placebo effect works

- **In scientific research → the aim is to UNDERSTAND how the placebo effect works**





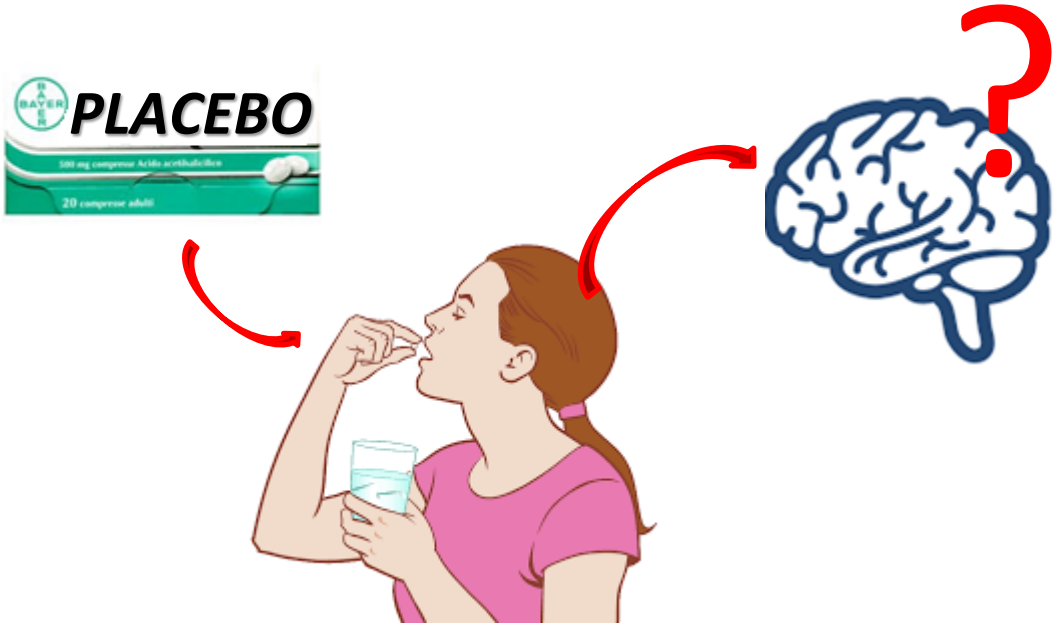


- **In clinical practice → the aim is to INCREASE the placebo effect**

Under what conditions does it work?

Pain

- Motor performance
- Parkinson's disease
- Alzheimer's disease
- Cardiovascular system
- Respiratory system
- Gastrointestinal System
- Immune system
- Endocrine system
- Depression
- Anxiety



Finniss et al. *Lancet* 2010;375:686-95

One of the most extensively studied systems in placebo research is the pain system

Enhance placebo: wrong
Block placebo effect: true
Block placebo effect of opioid drugs: true
Block placebo effect of non-opioid drugs: false

NALOXONE
μ antagonist

ISCHEMIC PAIN **OPIOIDS**

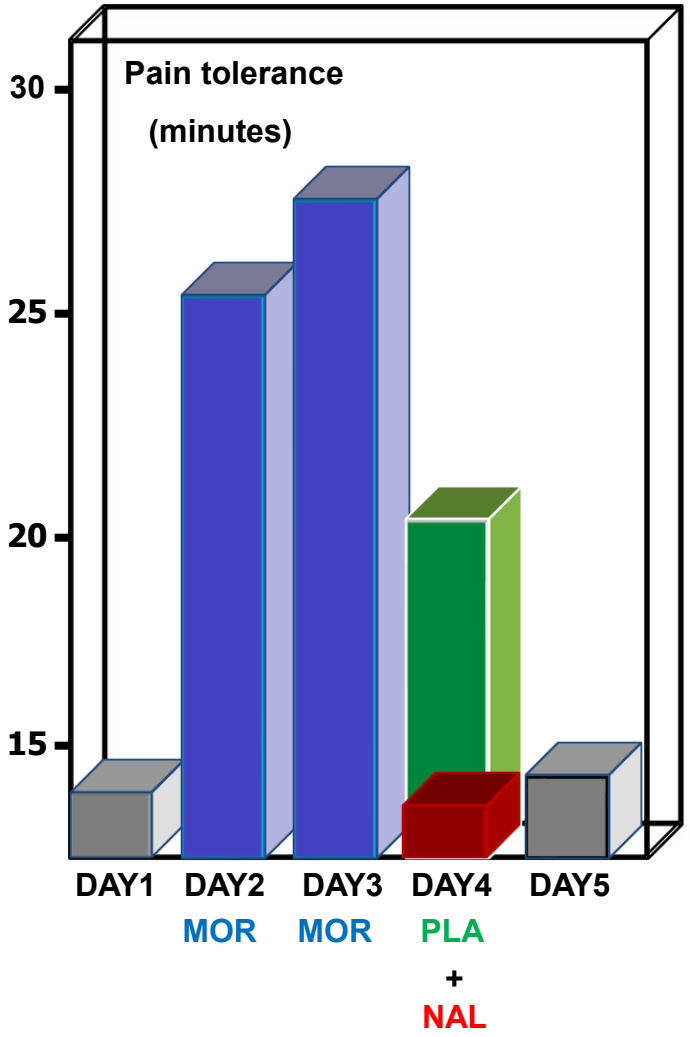
Placebo analgesia: Study on Ischemic Pain

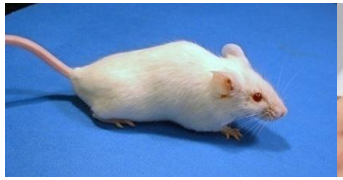
(Amanzio & Benedetti *J Neurosci* 1999; 19:484-94
Benedetti et al. *J Neurosci* 2007; 27:11934-9)

- **Day 1 (baseline):** no treatment → normal pain tolerance
- **Day 2 and 3:** morphine → augmented pain tolerance
- **Day 4**: Told morphine, Given **placebo** + **naloxone** (opiod antagonist) → pain tolerance returns to baseline

What we observe is that participants no longer respond to the placebo, and their pain increases (similar to day one).

→ HERE, PLACEBO EFFECT IS BLOCKED BY NALOXONE

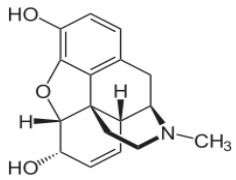




MICE

OPIOIDS

HOT PLATE TEST



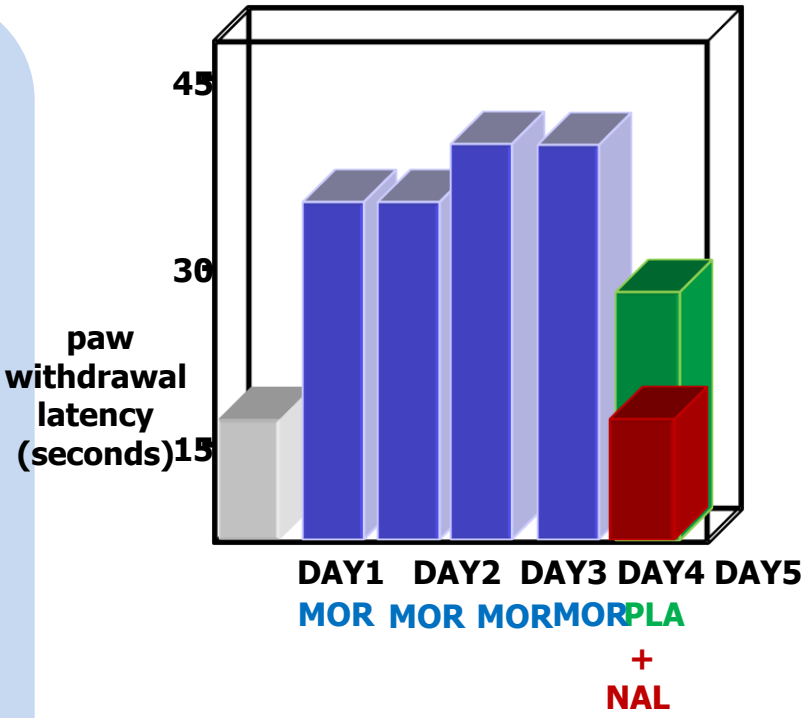
Drug (US) + blue light (CS)

Placebo analgesia: Animal Study (Mice)

- Mice reveived morphine paired with blue light (conditioning)
- On a hot plate test, pain tolerance increases after morphine
- With placebo + blue light →pain tolerance increases vs baseline (less than morphine)
- **With naloxone → placebo response is blocked**

→ Blockade of endogenous opioid abolishes the placbeo effect

→ **Could Placebo analgesia** be **mediated by endogenous opioid mechanisms?**

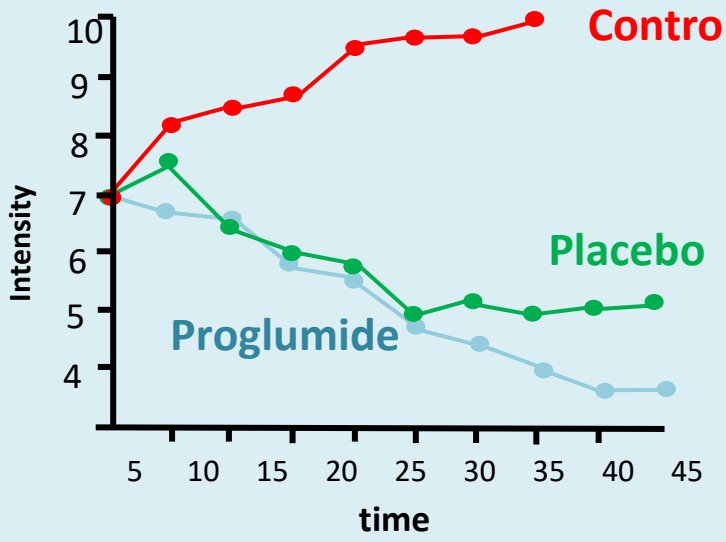


Guo et al. (2010) *J. Psychopharmacol.* 24: 1561-1567

PLACEBO ANALGESIA AND ENDOGENOUS OPIOIDS: CCK MODULATION

CCK (ANTI-OPIOIDS)

PROGLUMIDE (CCK antagonist)

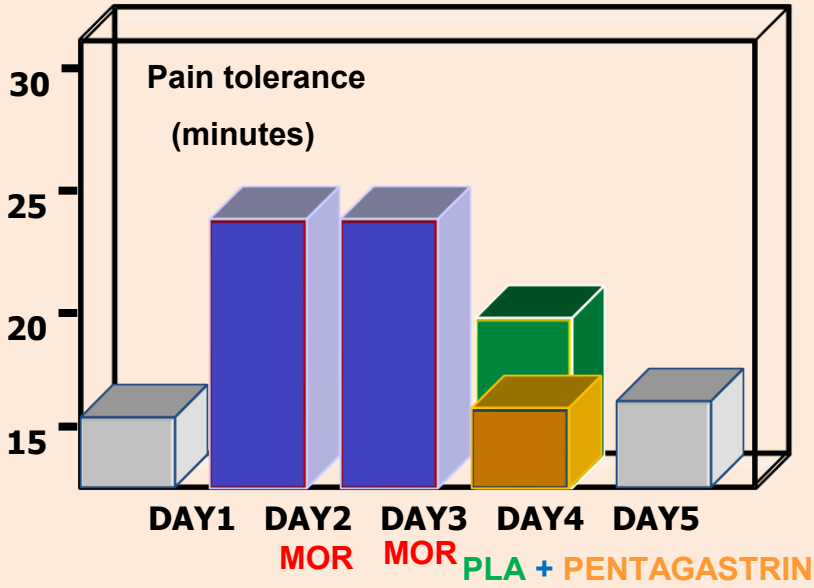


Proglumide (CCK antagonist):

- CCK normally inhibits endogenous opioids
- Blocking CCK → enhances endogenous opioid production and availability
- Result: **stronger placebo effect due to more free opioid receptors**

Benedetti et al. Lancet, *1995;* 346:1231.

PENTAGASTRIN (CCK agonist)



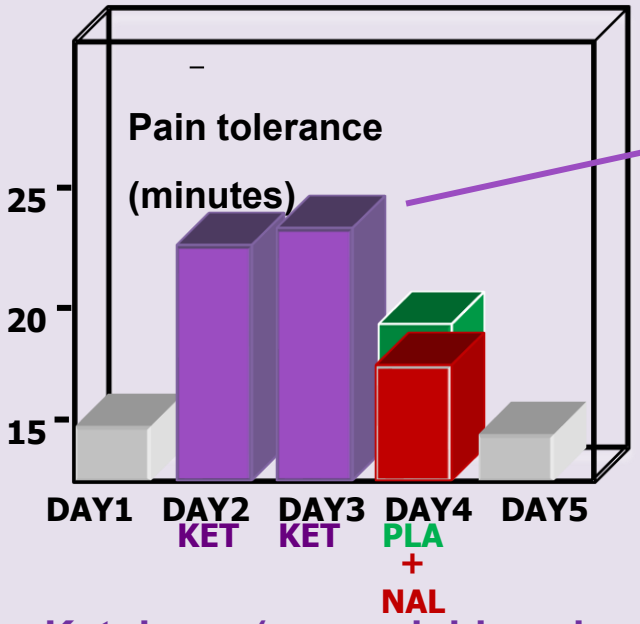
Pentagastrin (CCK agonist):

- Mimics naloxone effect → blocks placebo effect
- Activates CCK → inhibits endogenous opiodis → opioid receptors unavailable

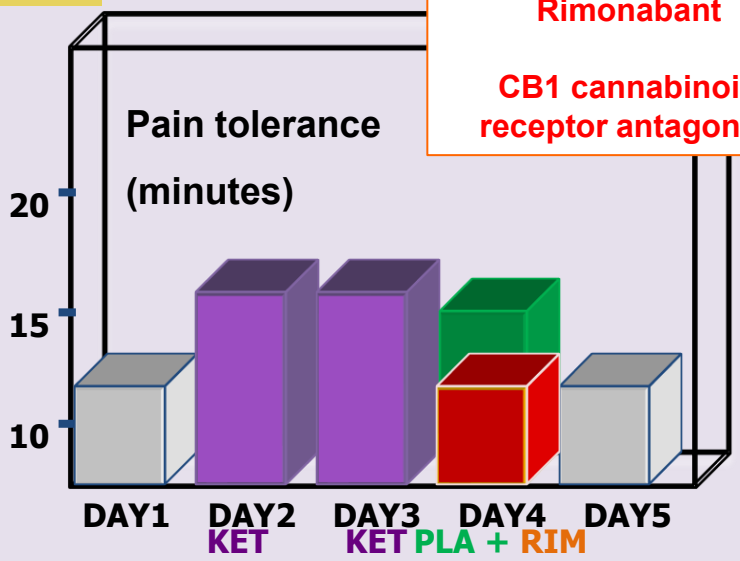
Benedetti et al. *Psychopharmacol* 2011; 213:791-7

PLACEBO ANALGESIA: NON-OPIOID ANALGESICS AND CB1 SYSTEM

CANNABINOIDS



Activation of CB1 receptor → < pain



Ketolorac (non-opioid analgesic):

- Reduces pain **via CB1 cannabinoid system**
- Preconditioning with ket → increases pain tolerance
- Placebo + naloxone → placebo effect still occurs, naloxone has no effect

→ The placebo effect here is not opioid-mediated.

Rimonabant (CB1 antagonist)

- Preconditioning with ketolorac→ increases pain tolerance
- Placebo + Rimonabant → blocks placebo analgesia

→ placebo effect is neurtotrasmitter specific

Amanzio & Benedetti *J Neurosci* 1999;19:484-94

Benedetti et al. *Nature Med* 2011;17:12828-30

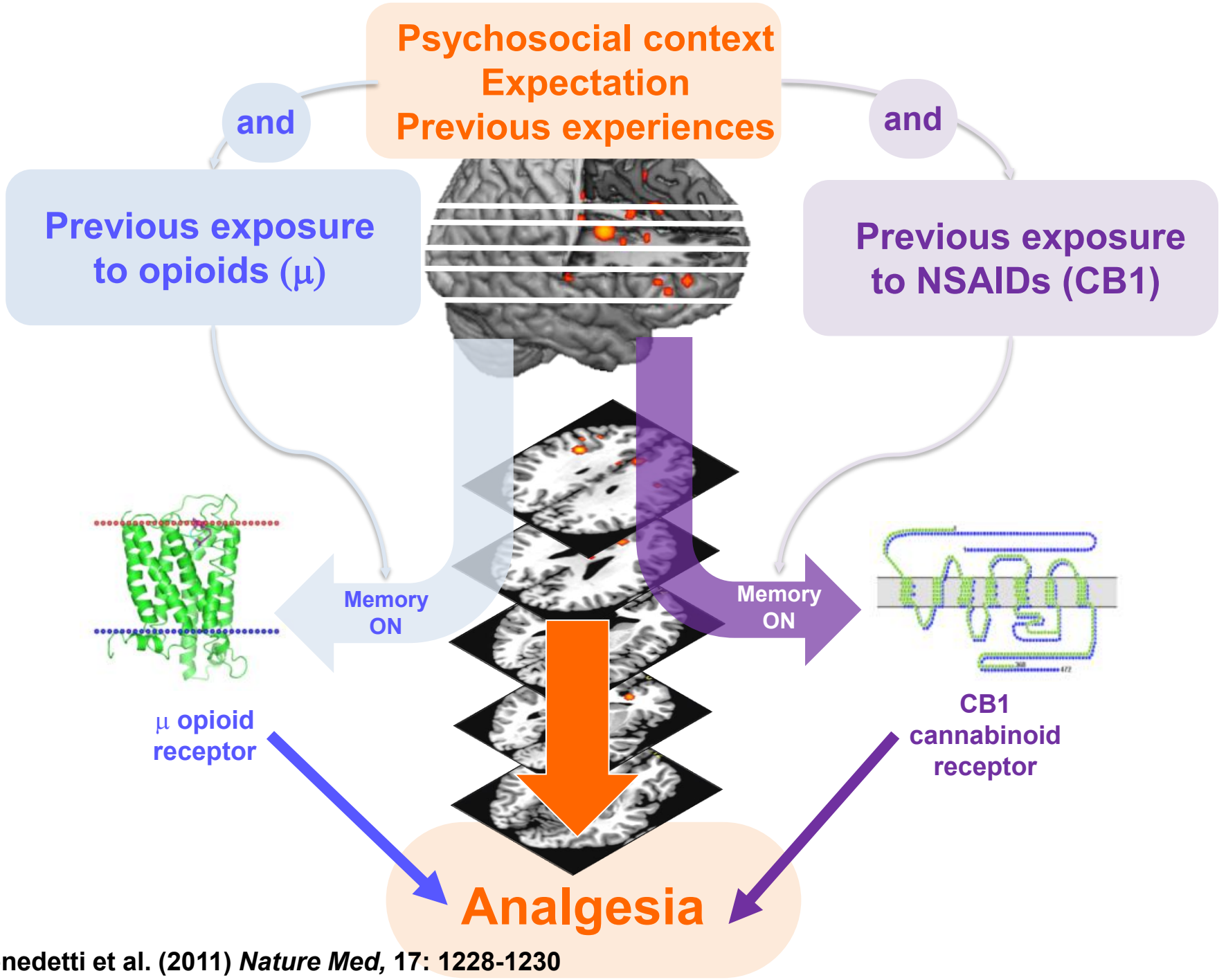
Placebo analgesia depends on the neurotransmitter system engaged during preconditioning

- If preconditioned with opioids → blocked with naloxone
- If preconditioned with cannabinoids → blocked by rimonabant

→ Past experiences, expectations, and psychosocial context can trigger analgesia via the **"drug memory"** mechanism.

→ The brain "remembers" drugs that produced analgesia previously. When a person expects the drug, endogenous opioids or cannabinoids are released, bind to their specific receptors, and induce analgesia **even without the actual drug**.

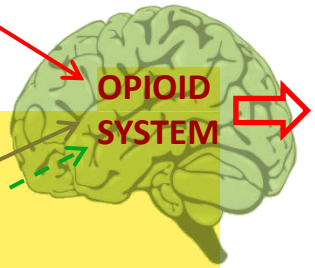
→ In other words, placebo analgesia depends both on the drug itself and on the memory of its effects.



Benedetti et al. (2011) *Nature Med,* 17: 1228-1230

Amanzio & Benedetti *J Neurosci* 1999
Benedetti et al. *J Neurosci* 2007
Benedetti et al. Lancet, *1995*
Benedetti et al. *Psychopharmacol,* 2011
Benedetti et al. *Nature Med* 2011
Kessner et al., Jama, 2013

Oppioid drugs
(e.g. morphine)



ANALGESIA

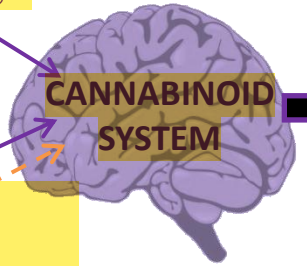
Placebo

Increased by anti-CCK drugs (e.g. proglumide)

- Block by anti-oppioid drugs (e.g. **naloxone**)

- Block by CCK agonist (e.g. **pentagastrine**)

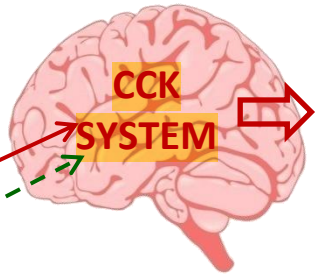
Cannabinoid drugs
(e.g. Ketorolac)



ANALGESIA

Placebo

- Block by anti-cannabinoid drugs (e.g. **rimonabant**)



HYPERALGESIA

Nocebo

Block by anti-CCK drugs (e.g. proglumide)

ANALGESIA

Placebo

OSSITOCINA E VASOPRESSINA

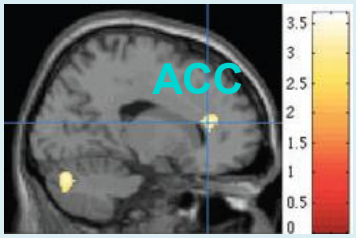
Placebo effect and PAIN

- Behavioral Studies
- Pharmacological studies
- Neuroimaging studies
  - PET-fMRI
  -EEG

PET AND fMRI STUDIES

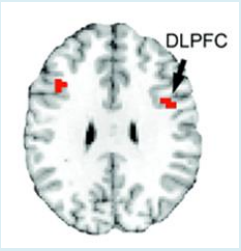
Opioid-induced analgesia and placebo analgesia activate the same brain areas

Increased activity in the Anterior cingulate cortex both in opioid analgesia and in placebo analgesia



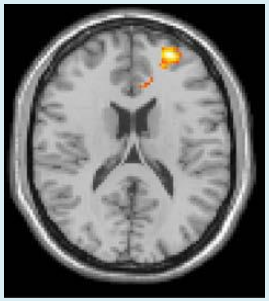
Petrovic et al. 2002 *Science* **295**: 1737-1740.

Pre-frontal mechanisms trigger opioid release in the midbrain



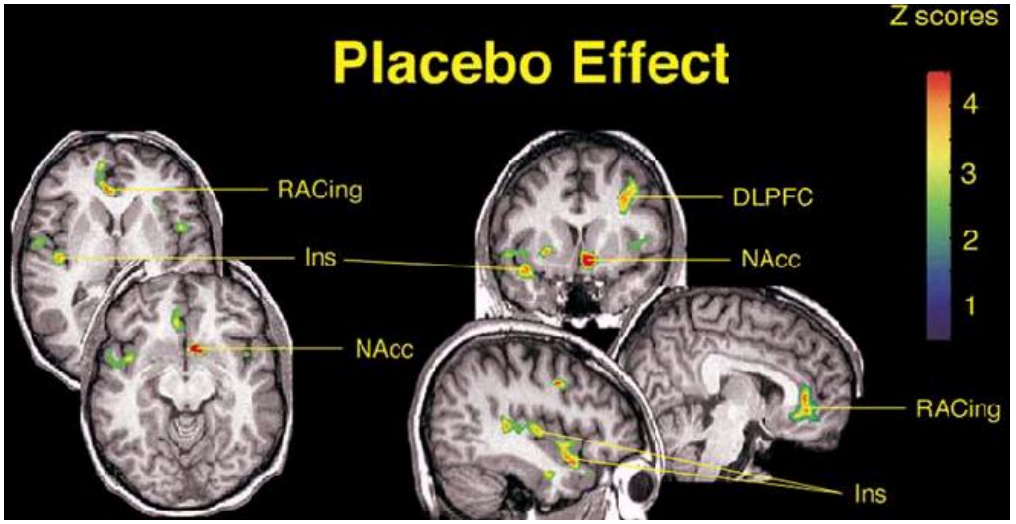
Wager et al. 2004 *Science* **303**: 1162-1167.

DLPFC



Identical areas were modulated during anticipation in the placebo analgesia phase and in the placebo conditiong phase (Dorsolateral prefrontal cortex)

Watson et al. 2009 *Pain* **145**: 24-30.



Zubieta et al. 2005 *J. Neurosci*. **25**: 7754 –7762.

Placebo effect is driven by the activation of prefrontal lobe: yes
the ACC is a mediator of placebo analgysia? yes Does the rdlPFC? yes

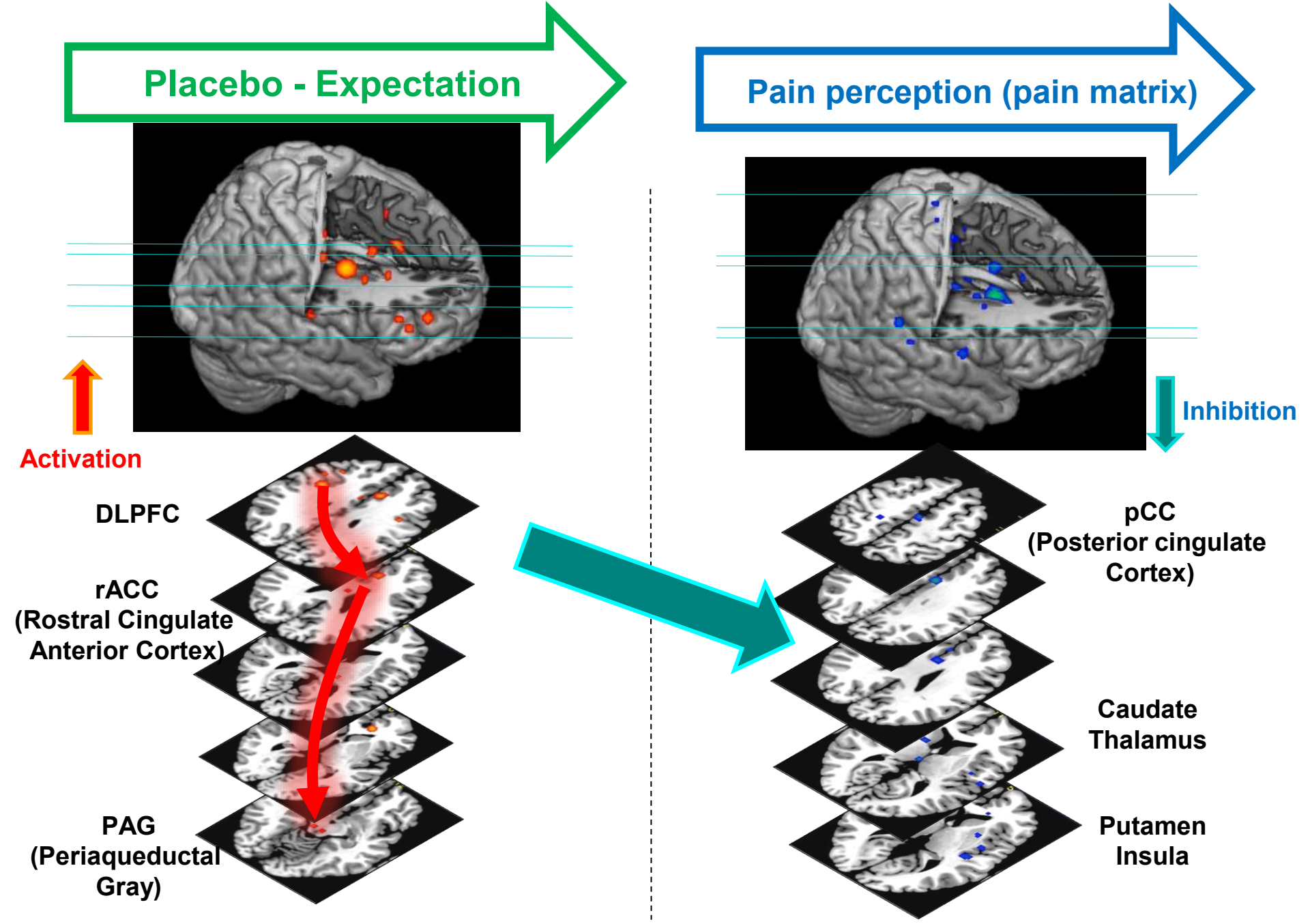
Role of DLPFC in Placebo Analgesia

Key Points:

- **Maintains the "placebo effect"**: helps sustain the expectation of analgesia.
- **Reduces pain perception**: even when the actual pain intensity is the same as baseline.
- **Consolidates priors**: triggers endogenous analgesic mechanisms based on prior drug experience.
- **Sensory modulation**: decreases incoming pain signals when no active drug is administered.

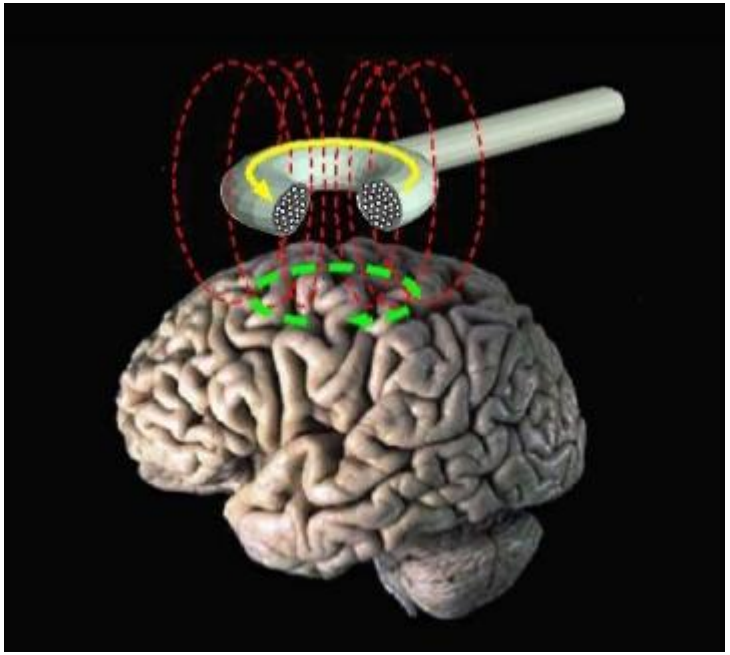
Implication:

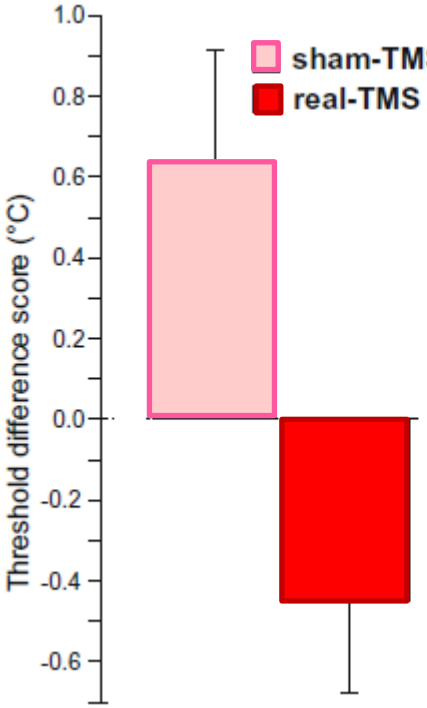
In placebo analgesia studies, **greater DLPFC activity** indicates stronger cognitive control over pain perception.



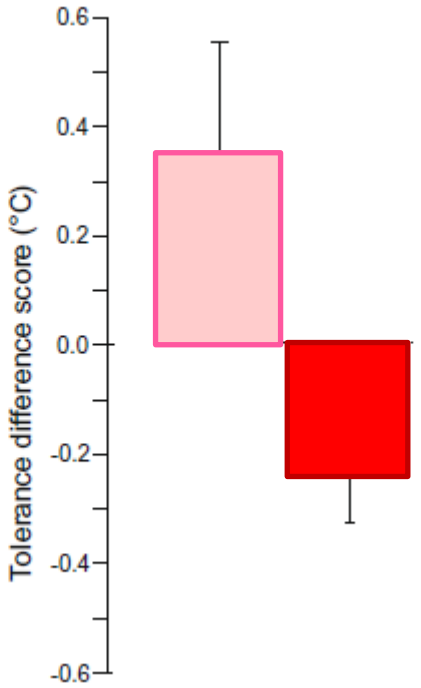
Amanzio, Benedetti et al (2011) *Hum Brain Mapp*

If the prefrontal area (DLPFC) is inactivated, placebo effect is abolished





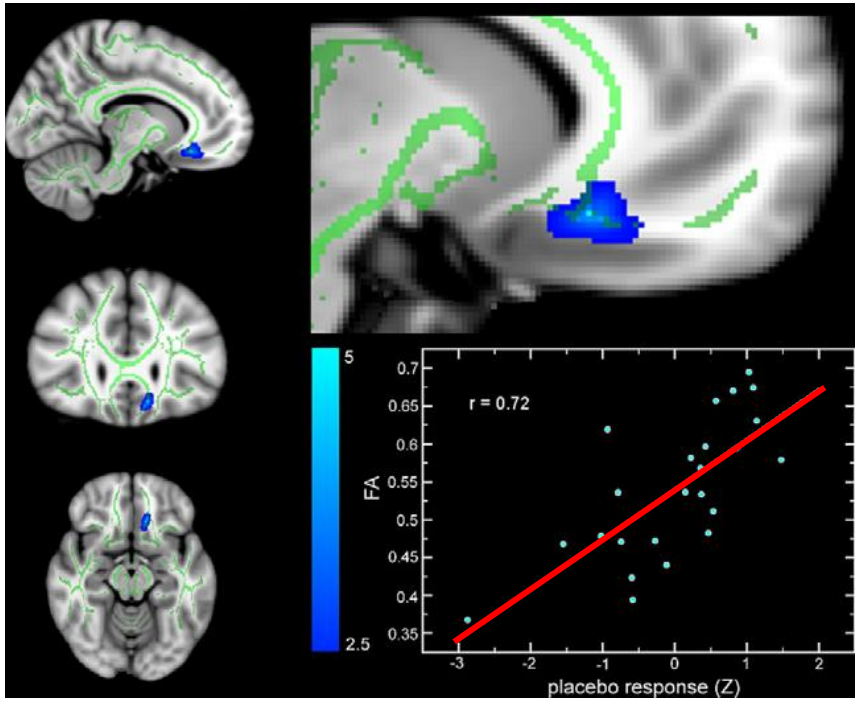
Analgesia expectation



Analgesia expectation

Krummenacher *et al.* 2010 ***Pain*** 148: 368-374

Lower frontal integrity corresponds to a lower placebo response



The matter integrity by fractional anisotropy in normal subjects

Stein et al (2012) *Pain* 153: 2210-2217

THE EFFECT OF TREATMENT EXPECTATION ON DRUG EFFICACY

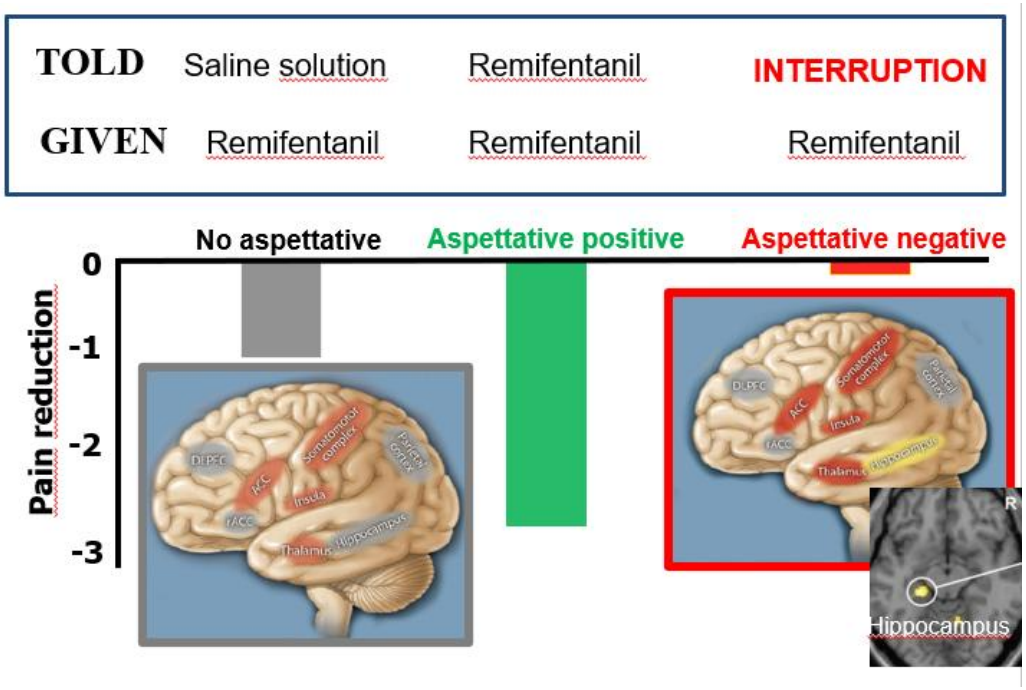
All participants received remifentanil, at a fixed dose.

The study aimed to test how expectations modulate the effect of a real drug:

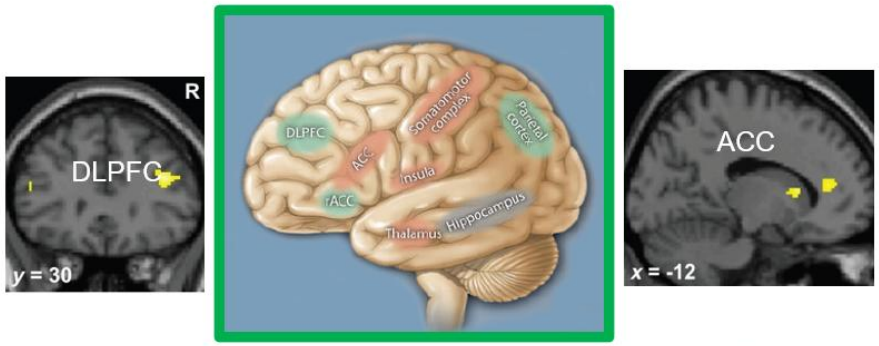
1. **No expectancy:** patients received remifentanil without knowing its effect
2. **Positive expectancy:** participants received remifentanil and, therefore they expected pain relief
3. **Negative expectancy:** participants received remifentanil but thought they were not receiving it anymore

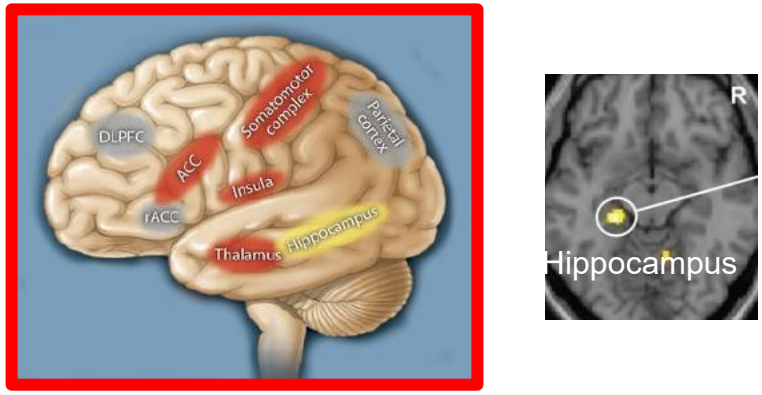
Open-hidden paradigm: in it when you give a real drug hidden the effect of the drug are higher compared to the open adiministration: fasle

If you give drug without the awareness you don't give the patience the contextual factors, so he doesn't expect a real effect (reduction of the drug effect, becaue you remove the placebo component.



Bingel *et a*l. 2011 *Science Trans Med,* **3**: 70ra14
Gollub and Kong, 2011 *Science Trans Med* Com





OPEN ADMINISTRATION:

- Expecting pain relief enhances opioid analgesia
- Brain activity increases in:
  - **Dorsolateral prefrontal cortex** (DLPFC)
  - **ACC** (anterior cingulate cortex)
  - **Striatum** (Caudate, putamen)
  - **Frontal operculum**

HIDDEN ADMINISTRATION:

- Expecting more pain reduces opioid analgesia
- Brain activity increases in:
  - **Pain network**: S1, MCC (mid cingulate cortex), insula, thalamus
  - **Hippocampus, amygdala, MPFC, cerebellum**

Bingel *et a*l. 2011 *Science Trans Med,* **3**: 70ra14
Gollub and Kong, 2011 *Science Trans Med* Com

Placebo effect and PAIN

- Behavioral Studies
- Pharmacological studies
- Neuroimaging studies

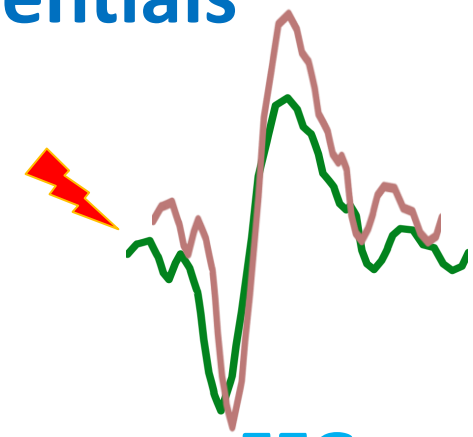
  - PET-fMRI
  - EEG

Placebo and Event Related Potentials (ERPs)

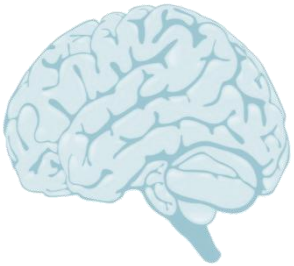
- STUDY 1: LEP

(Laser-Evoked Potentials)

early nociceptive processes



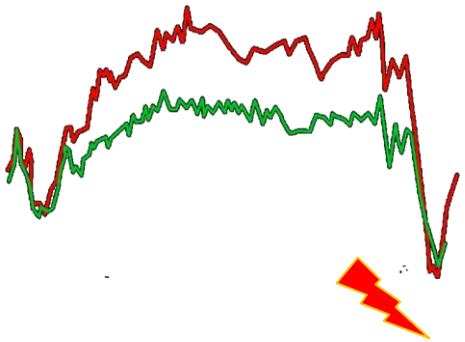
EEG



- STUDY 2: CNV

(Contingent Negative Variation)

anticipation phase during pain-task

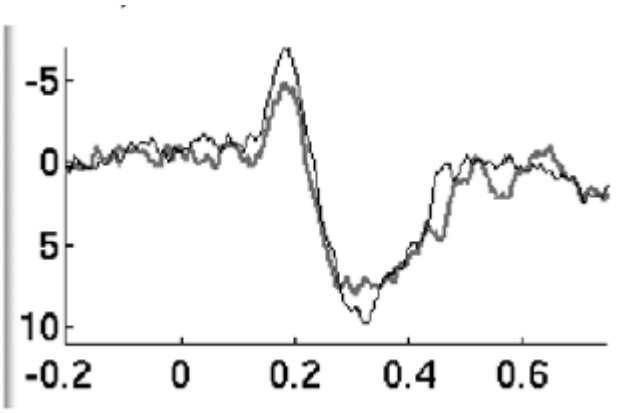


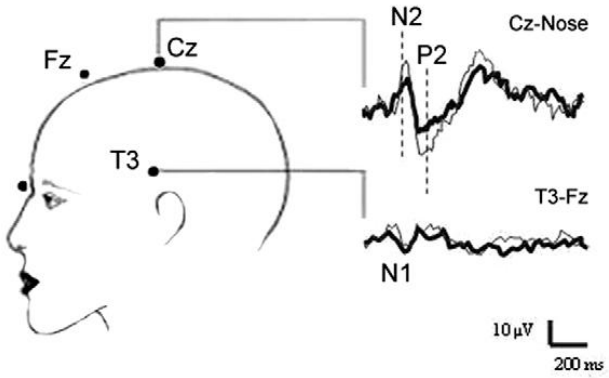
DECREASE IN N2-P2 complex during placebo analgesia

The **N2–P2 complex** is a component of laser-evoked potentials (LEPs) that reflects **cortical processing of painful stimuli**, particularly the **conscious perception and evaluation of pain**.

In this study, both **verbal suggestion** and **conditioning** altered the N2–P2 complex, indicating a change in how the brain processes pain signals.

However, only conditioning led to a **reduction in perceived pain**, suggesting that **learning through prior positive experience** (rather than expectation alone) modulates pain both **neurophysiologically and subjectively**.





Colloca et al. Pain 139 (2009) 306-314
Wager et al. Brain, Behav Imm 20 (2006) 219-230
Watson et al Pain 126 (2006) 115-122

CONDITIONED ANALGESIA AND THE ROLE OF VERBAL INFORMATION

ACQUISITION

Participants learn the association between visual cues and pain intensity.

– < INTENSITY — LESS PAIN

\+ > INTENSITY — MORE PAIN

COND + VER group

- Two conditioning blocks: **one cue paired with increased pain** and the other with **decreased pain**
- VER group receives information about the meaning of the cue,
- noVER group does not

EVALUATION

– = INTENSITY ?

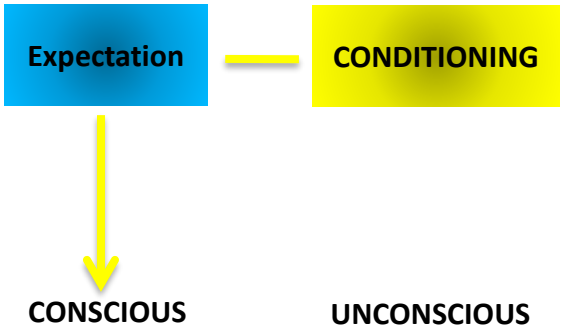
\+ ?

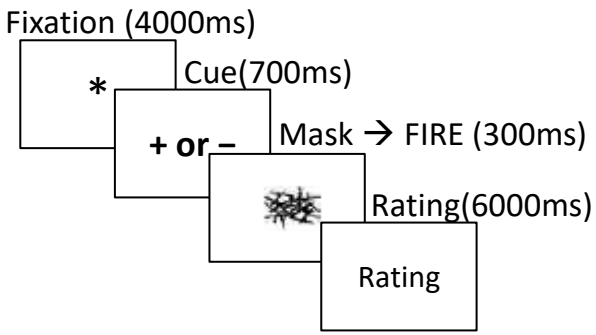
COND + NO VER group

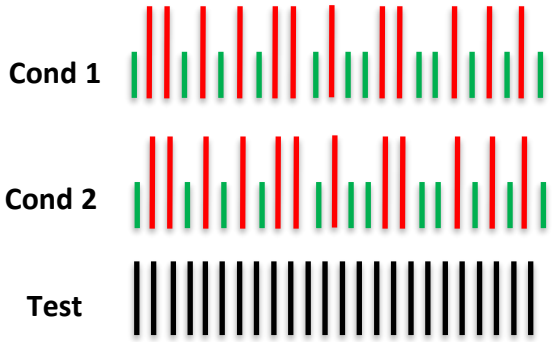
All cues are presented with the **same pain intensity**, regardless of the cue.

- Purpose: assess whether the association learned during acquisition affects pain perception.
- Measures: **pain ratings (0–10)** and **LEP N2–P2 amplitudes**.

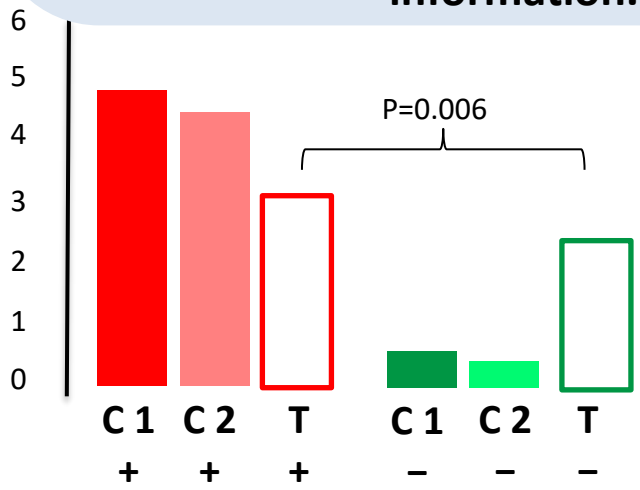
Carlino et al., EJP, 2015



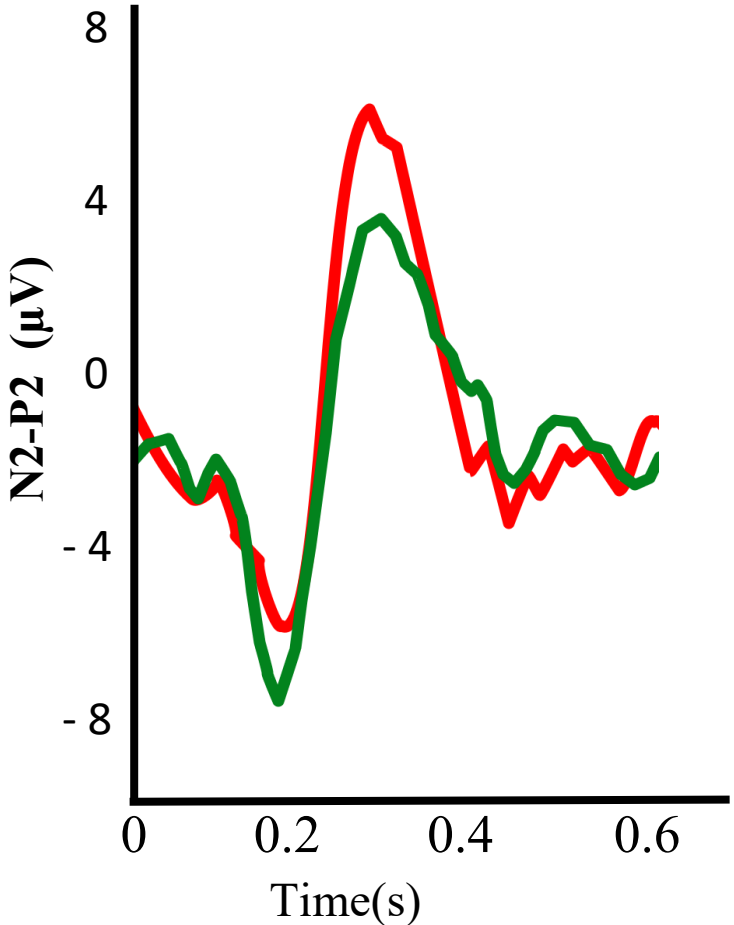




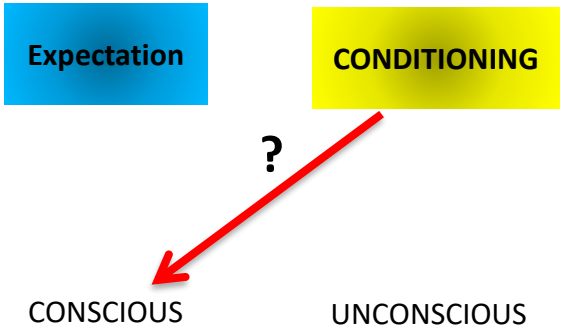
In the evocation session, only the **VER group** reported a decrease in pain rating and LEP amplitude when the cues were presented, suggesting that **the visual–analgesic association does not occur without explicit verbal information.**

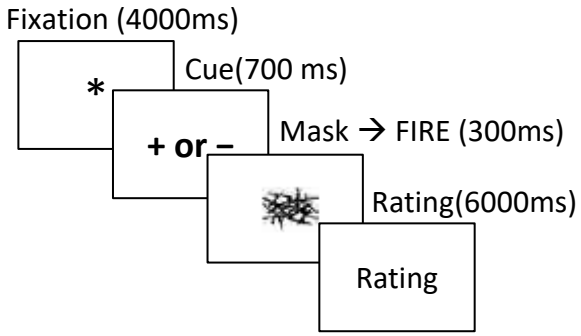


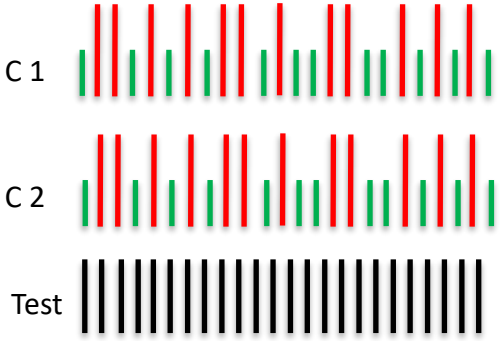
EFFECT

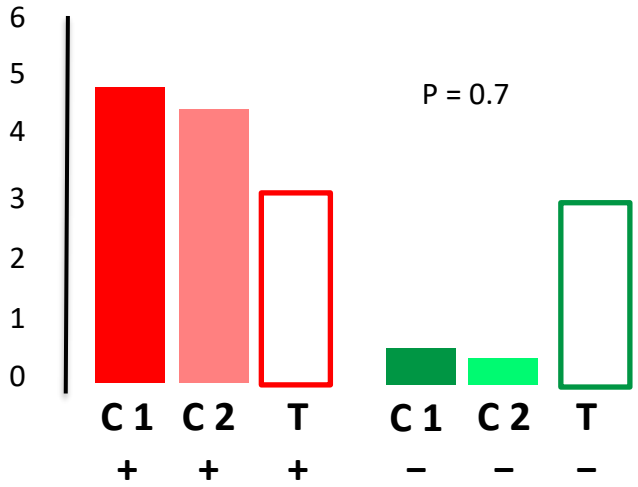


Carlino E, EJP, 2015

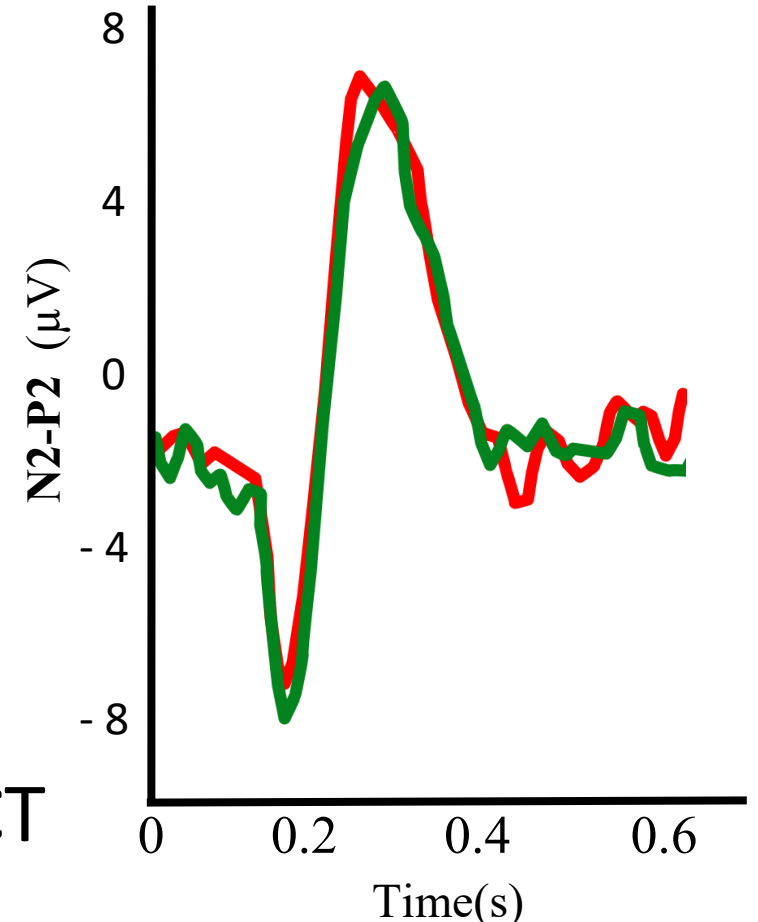








NO EFFECT

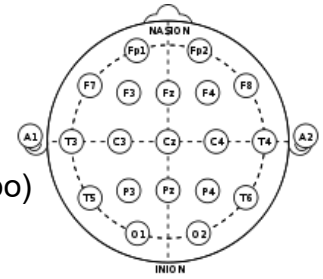


Carlino E, EJP, 2015

Another study investigates **how expectations modulate pain**, underlying **placebo hypoalgesia** and **nocebo hyperalgesia**.

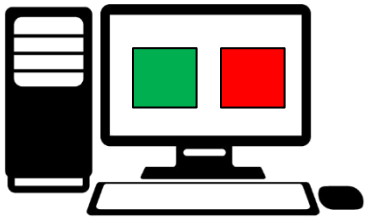
It is novel in using the **Contingent Negative Variation (CNV),** an electrophysiological marker of cognitive anticipation and motor preparation, to separate **sensory** and **motor components of pain**.

- **Experiment 1 (conditioning):**
  - Acquisition: cues paired with **non-painful (green)** or **painful (red)** stimuli.
  - Test: stimulus intensity kept constant to isolate expectation effects.
- **Experiment 2 (expectation only)**:
  - No conditioning; expectations induced by cues alone.
- **Measures**:
  - **CNV**: early (cognitive anticipation) and late (motor preparation) components.
  - **Pain ratings**: subjective perception.
  - **Reaction time**: time to stop painful stimulation.

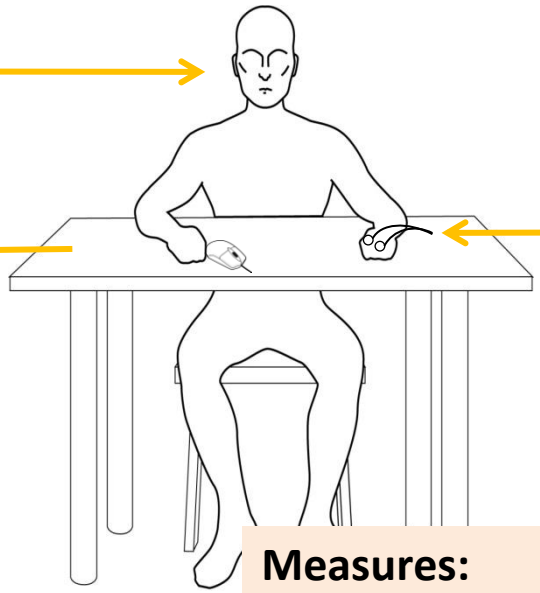


Green cue → expected pain reduction (placebo)
Red cue → expected pain increase (nocebo)

warning



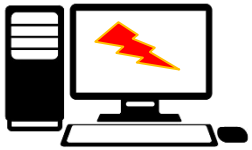
Cue's presentation



Reaction time recording

imperative

Electrical shocks



EEG recording

ACQUISITION

EVOCATION

COND group

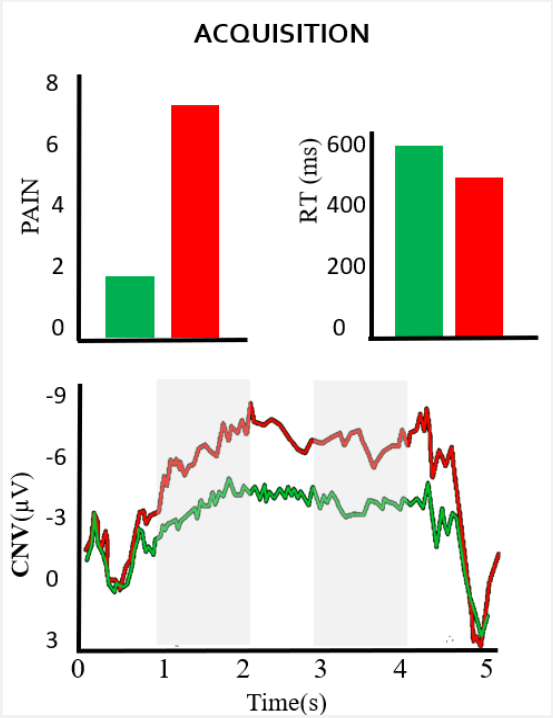
Measures:

- **RT:** reaction time to stop the stimulus

(if slower → no unconscious expectation of painful stimulus, if faster → unconscious expectation of painful stimulus)

- **Pain Rating:** Conscious, anticipatory system
- **EEG recording**

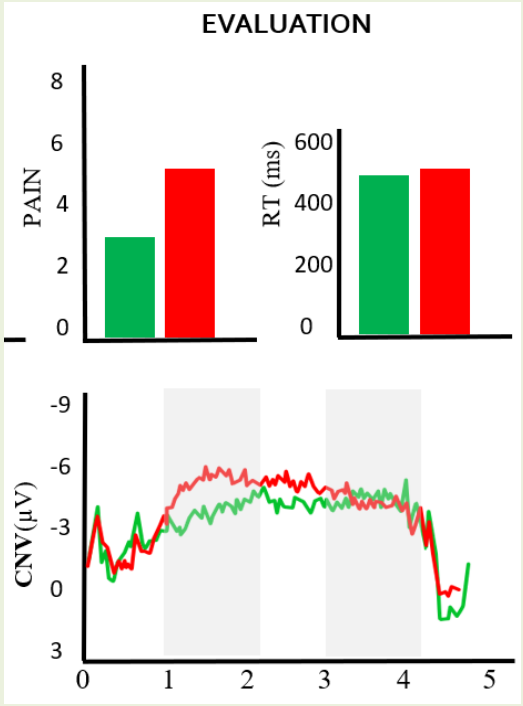
Piedimonte et al., 2017



Pain rating : increased with red cue → painful stimulus

Reaction time → decreased with red cue

CNV → red cue → bigger effect → more preparation to avoid the stimulus



Pain rating: increased with red cue → neutral stimulus

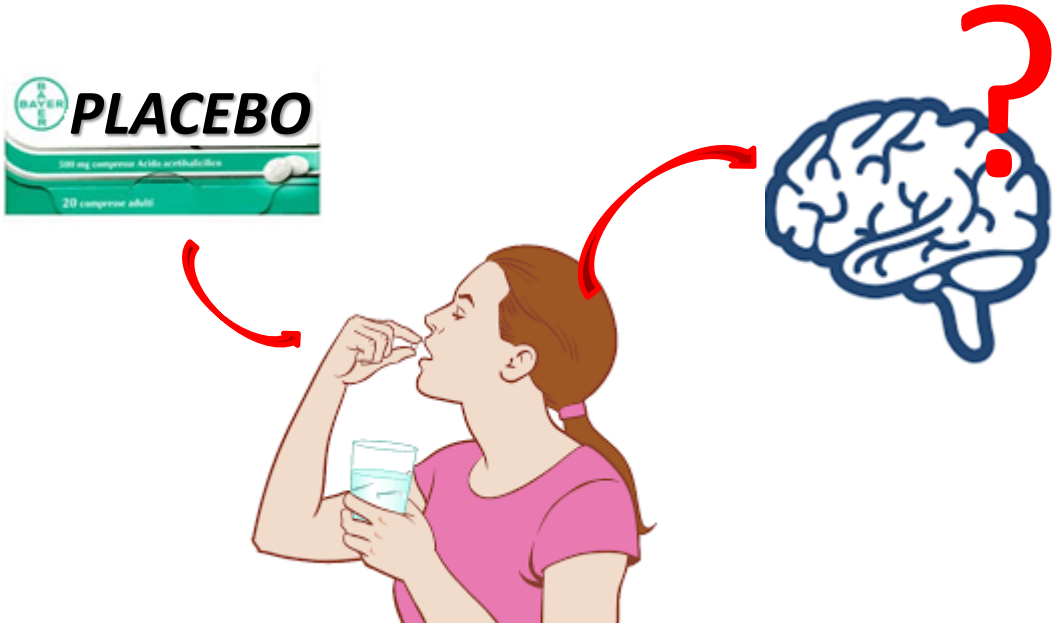
Reaction time → red cue = green cue

CNV → red cue → bigger effect only in the early one

The **conscious, anticipatory system** can be influenced by conditioning, whereas the **automatic motor system** is much harder to modulate

Under what conditions does it work?

- Pain
- Motor performance
- Parkinson's disease
- Alzheimer's disease
- Cardiovascular system
- Respiratory system
- Gastrointestinal System
- Immune system
- Endocrine system
- Depression
- Anxiety



Finniss et al. *Lancet* 2010;375:686-95

MOTOR SYSTEM

Placebo effect

(caffeine drink)

Nocebo effect

(sham stimulation)

Subjects performed different leg extension sessions, to exhaustion, in different days.

INDEXES:
- work performed
- fatigue

PROTOCOL 1:
Expectation alone

SESSION 1
Baseline

SESSION 2
Evaluation

PROTOCOL 2:
Expectation + conditioning

SESSION 1
Baseline

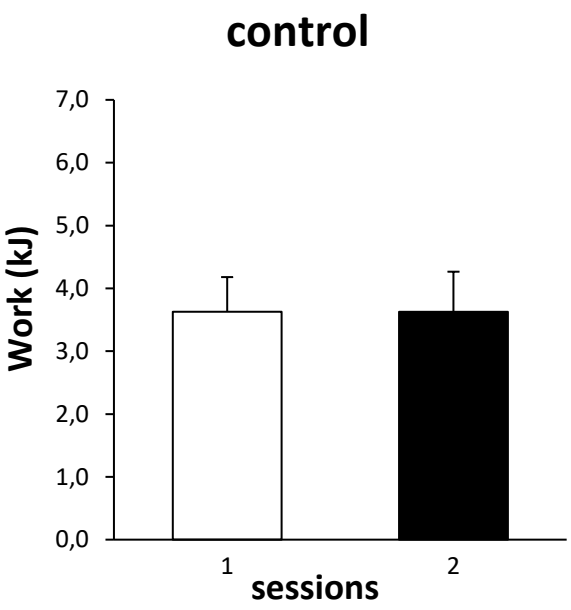
SESSION 2 and SESSION 3
Conditioning + Expectation

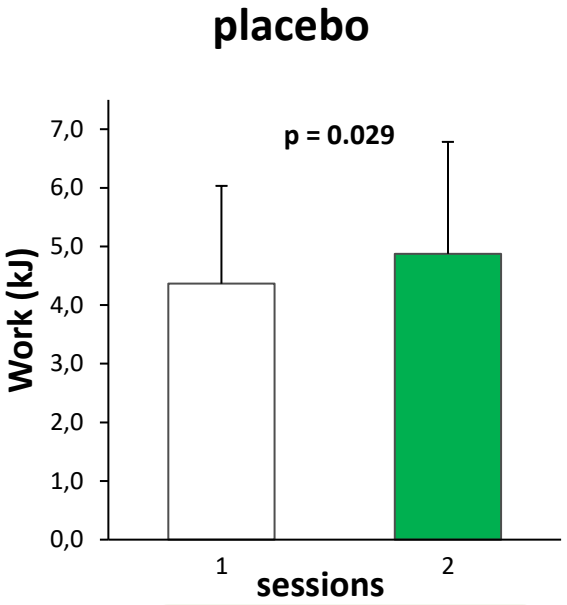
PLACEBO

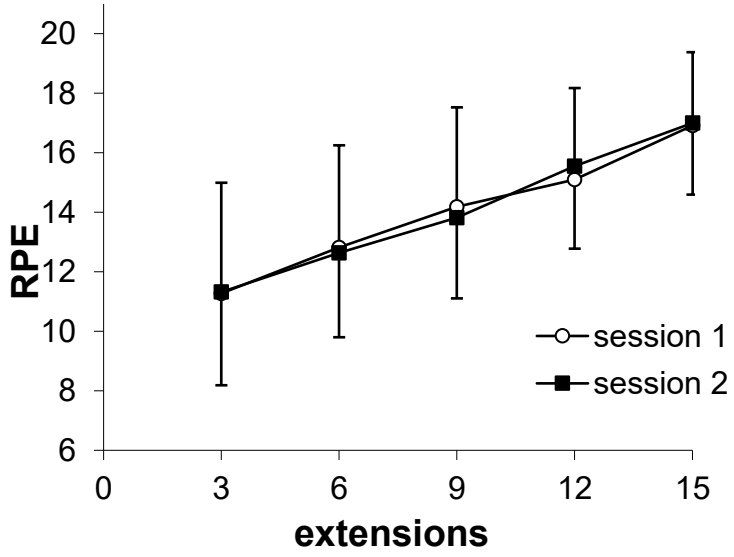
NOCEBO

SESSION 4
Evaluation

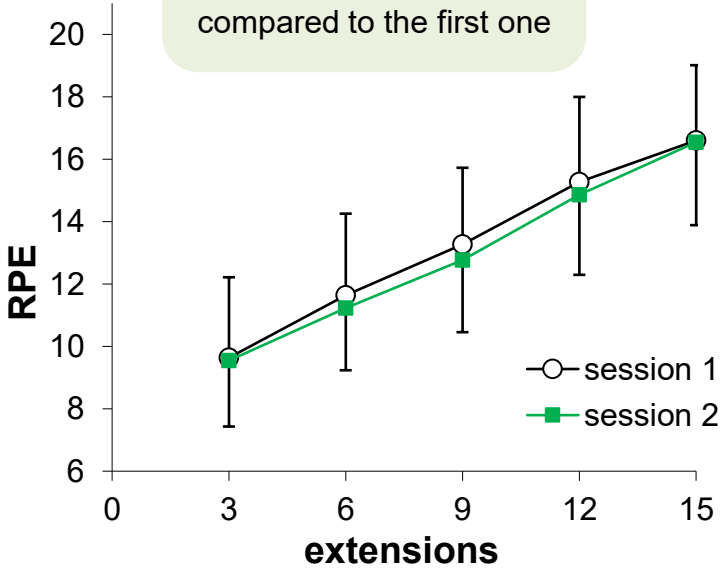
Pollo et al., 2008

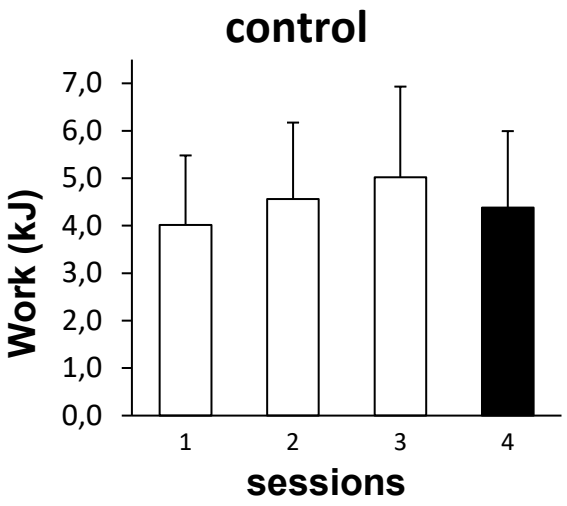


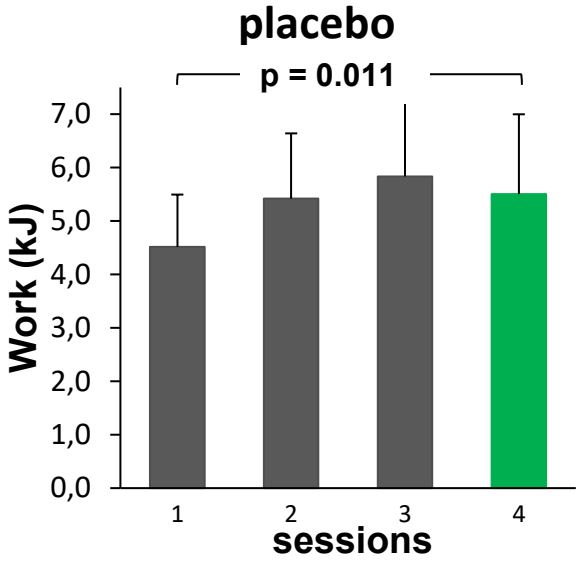


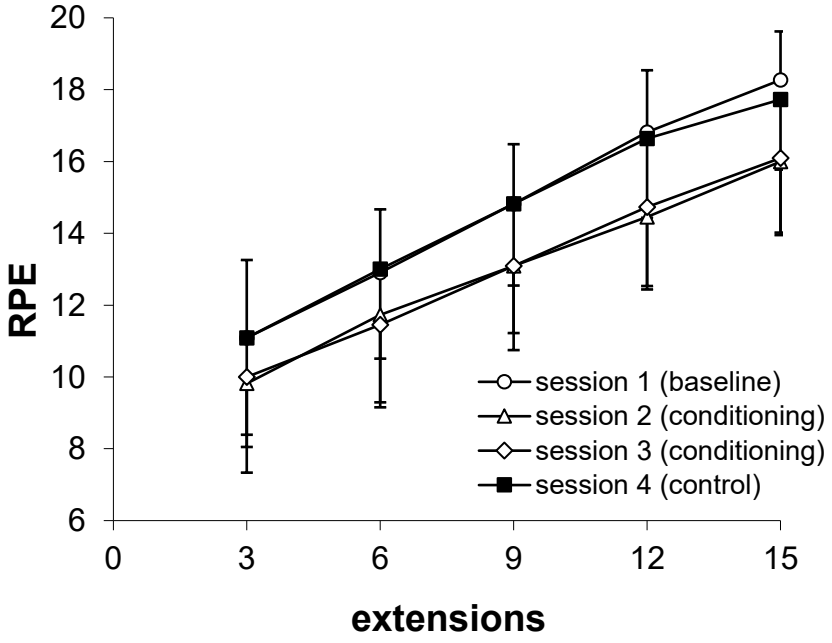


More work done and **less fatigue perceived** in the second session compared to the first one

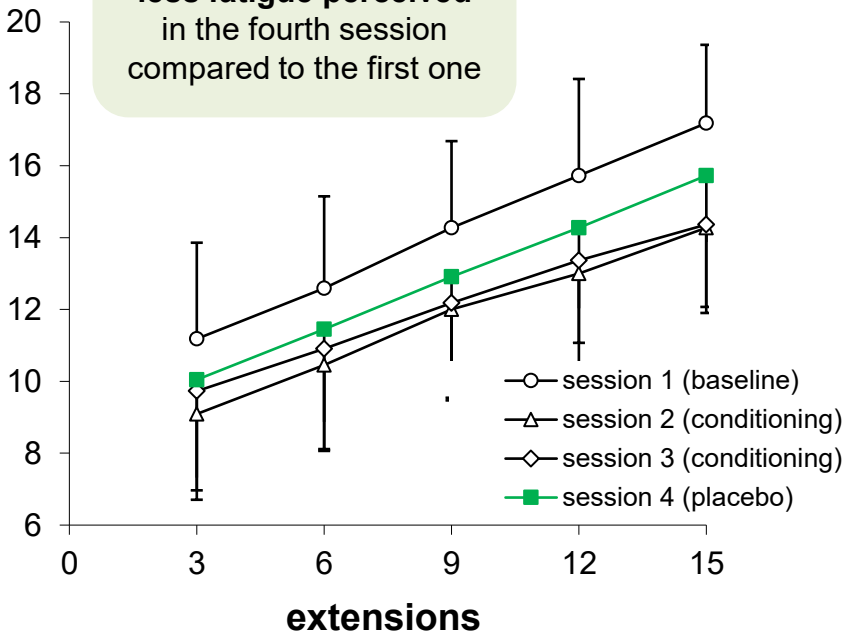








More work done and **less fatigue perceived** in the fourth session compared to the first one



Expectation protocol → patients showed **partial improvements:** they could do more repetitions, but their **fatigue level did not change**.

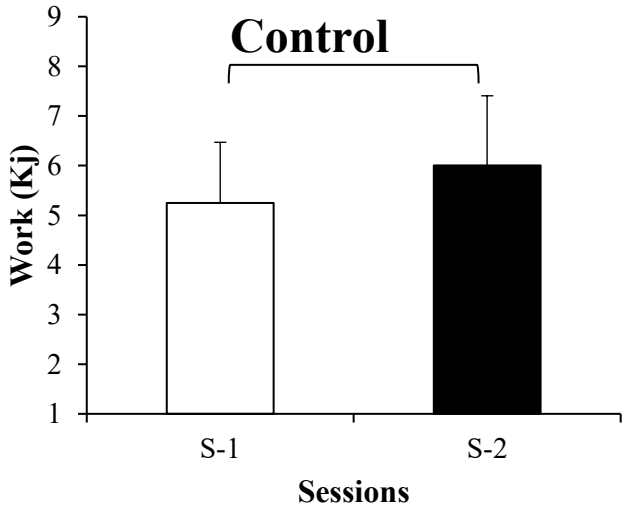
Conditioning protocol → there was a **clear improvement by session 4 (final phase), both in subjective (RPE) and objective (rep) measures**

CONCLUSION

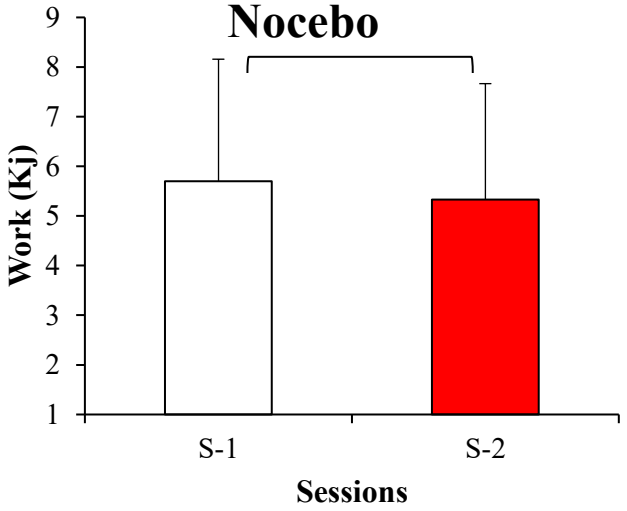
- The placebo effect acts on the motor system in "physiological" conditions
- The conditioning protocol induces greater effects than just expectation

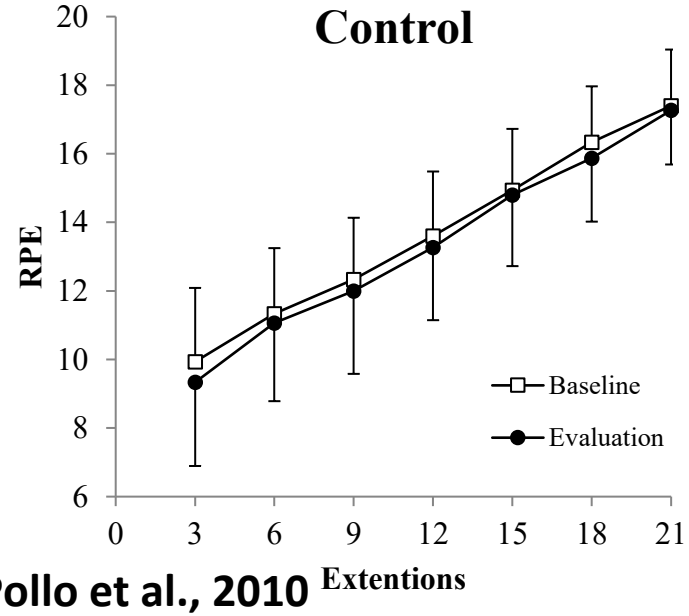
When we talk about motor placebo: improved motor performance, improvement of pain perception, or decrease in fatigue perception (?)

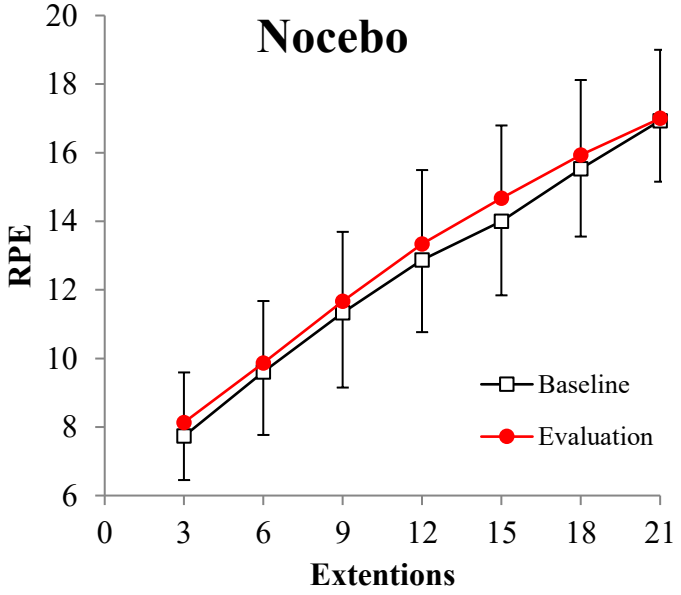
Improvement
in the Control Group



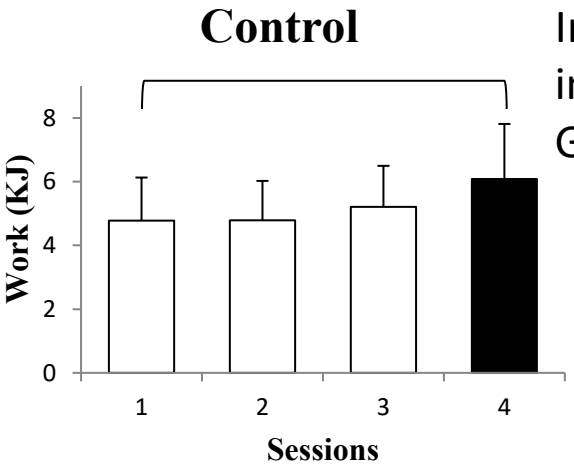
Worsening
in the Nocebo Group:
- Less work (rep)
- Higher RPE



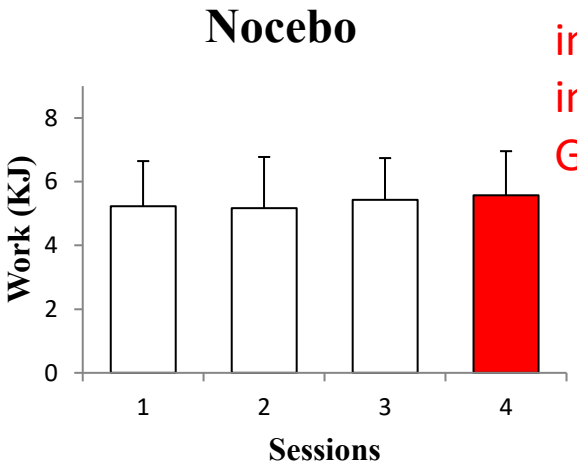




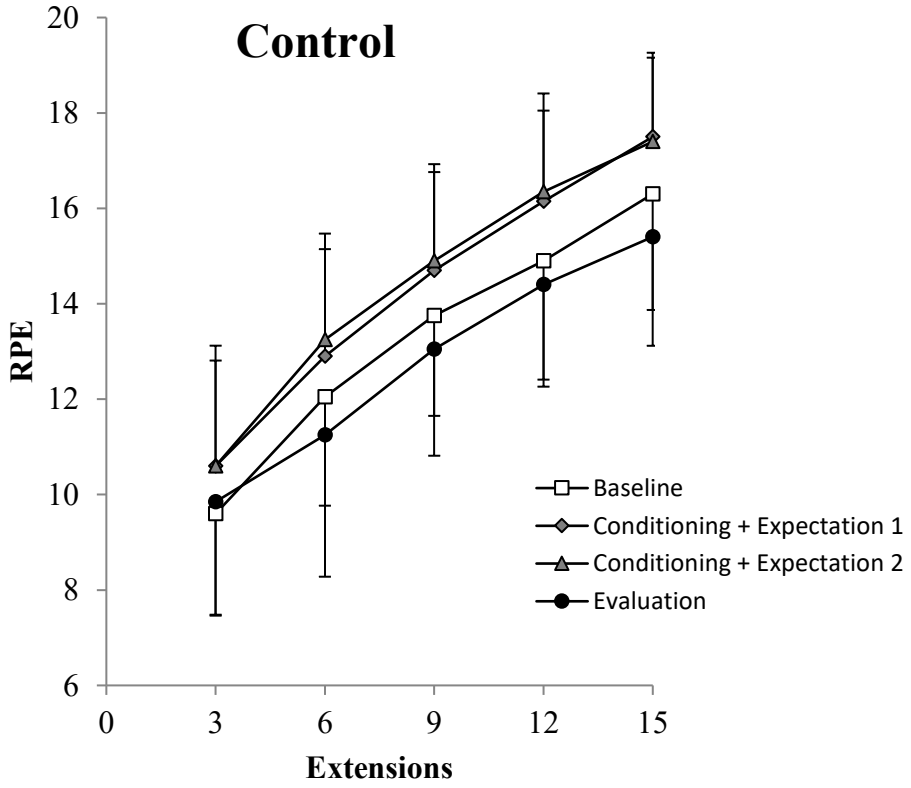
Pollo et al., 2010

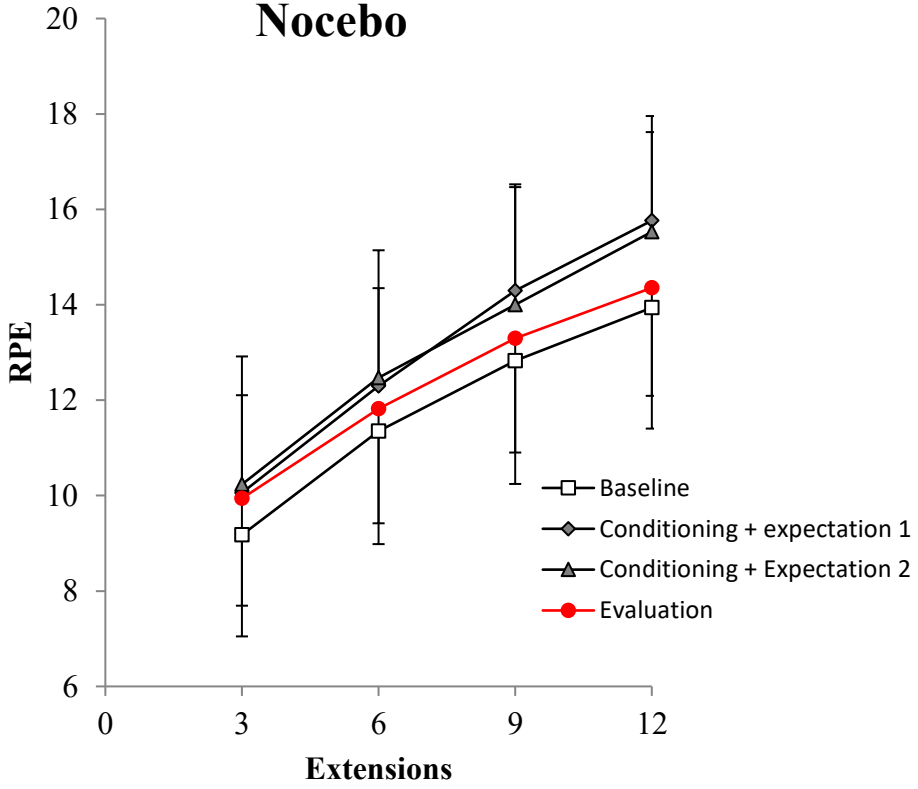


Improvement in the CONTROL GROUP



No improvement in the NOCEBO GROUP



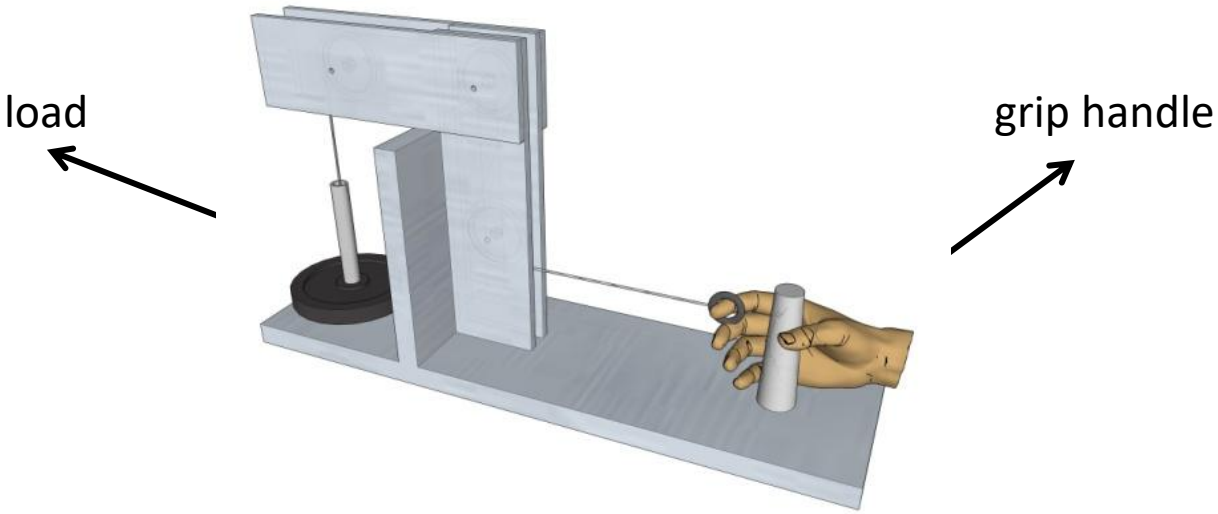


CONCLUSIONS

- The nocebo effect acts on the motor system in "physiological" conditions.

- **Expectation alone** produces a worsening of performance even without preconditioning

A)



B)

CONTROL GROUP

First series (10-min, 60 movements)	**Second series** (10-min, 60 movements)	**Third series** (10-min, 60 movements)

PLACEBO GROUP

First series (10-min, 60 movements)	**Second series** (10-min, 60 movements)	**Third series** (10-min, 60 movements)

☕ administration → ☕ expected effect → "in ten minutes it will be effective"

Piedimonte et al., 2015, European Journal of Neuroscience

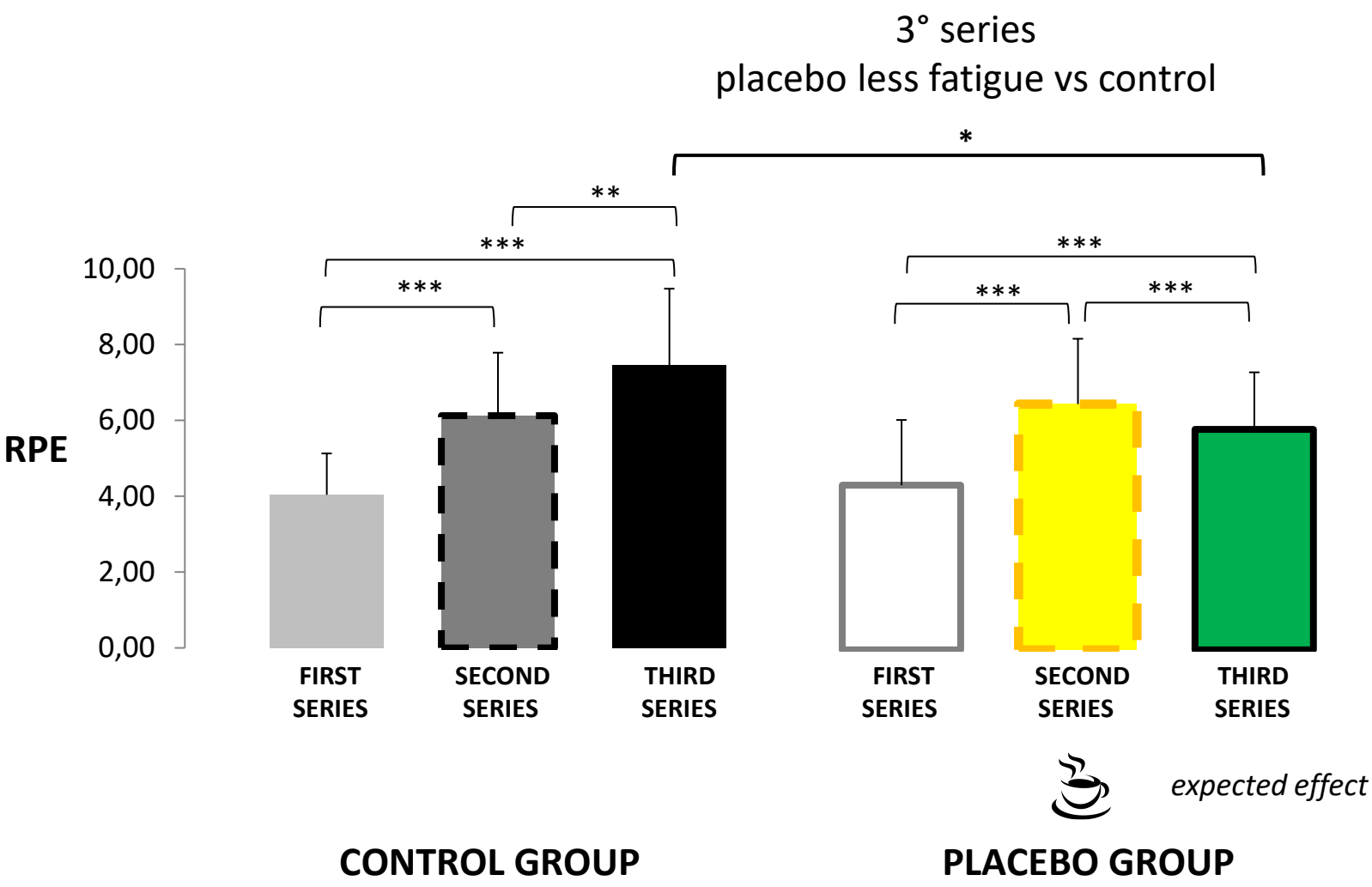

3° series
placebo less fatigue vs control
*
**
***
***
***
***
10,00
8,00
6,00
4,00
2,00
0,00
RPE
FIRST SERIES
SECOND SERIES
THIRD SERIES
FIRST SERIES
SECOND SERIES
THIRD SERIES
expected effect
CONTROL GROUP
PLACEBO GROUP

FIG. 2

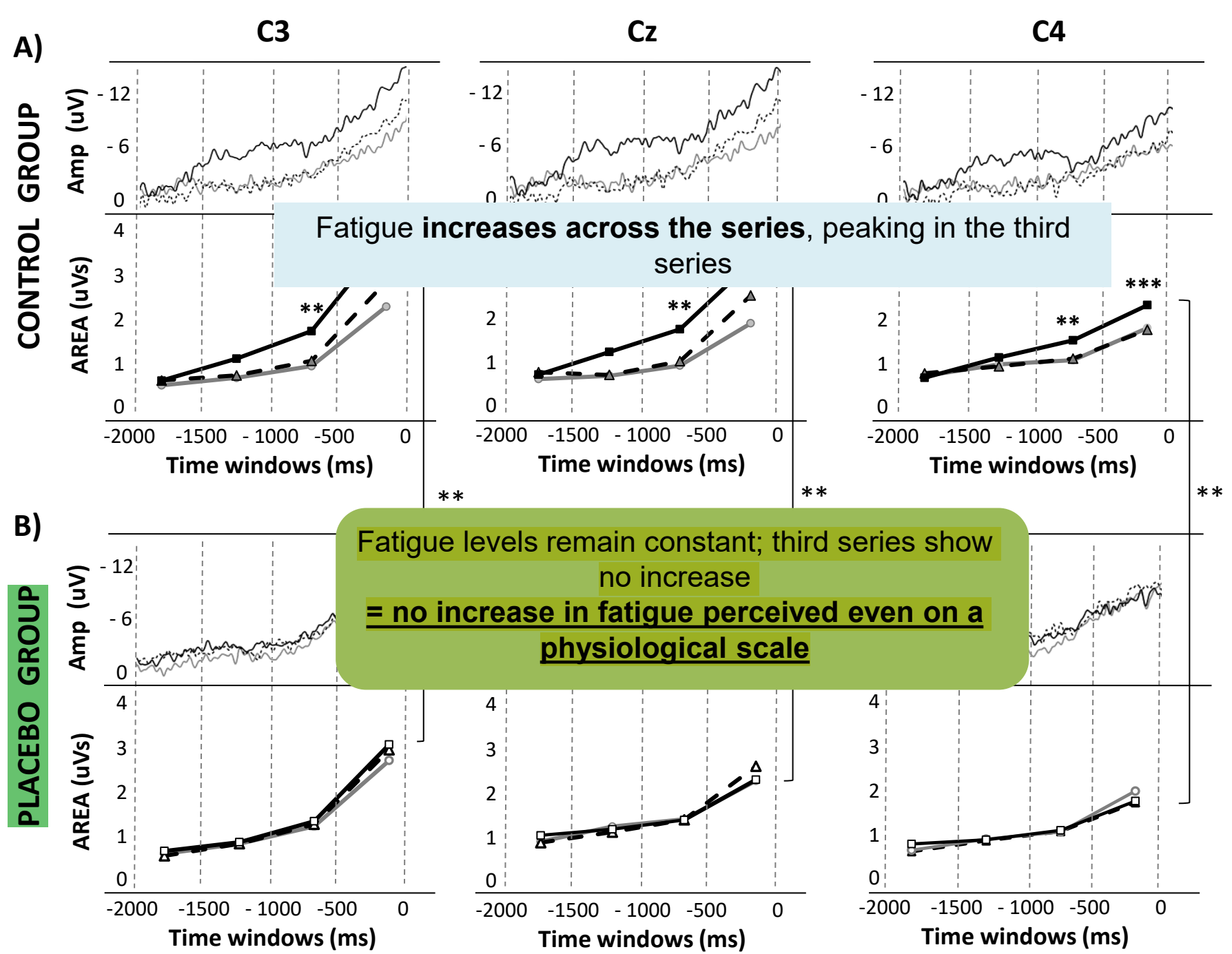

A)
CONTROL GROUP
C3
Cz
C4
Amp (uV)
- 12
- 6
0
AREA (uVs)
4
3
2
1
0
**
***
-2000
-1500
- 1000
-500
0
Time windows (ms)
Fatigue **increases across the series**, peaking in the third series
B)
PLACEBO GROUP
Fatigue levels remain constant; third series show no increase
= no increase in fatigue perceived even on a physiological scale
First series
Second series
Third series

FIG. 3

Conclusions

Placebos and nocebos

CENTRAL MECHANISMS

Facilitatory system

- Motor cortex
- Orbitofrontal cortex
- Prefrontal cortex
- Anterior Cingulate cortex
- Limbic system
- Thalamus
- Basal ganglia

Inhibitory system

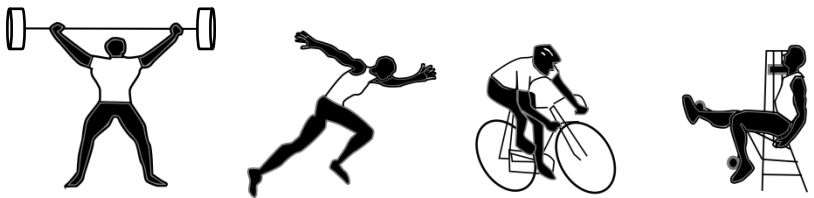
- Motor cortex
- Anterior Cingulate cortex
- Medial and posterior insular cortex
- Secondary somatosensory cortex
- Thalamus
- Spinal cord

PERIPHERAL SIGNALS

- Increase of motor output
- Decrease of fatigue

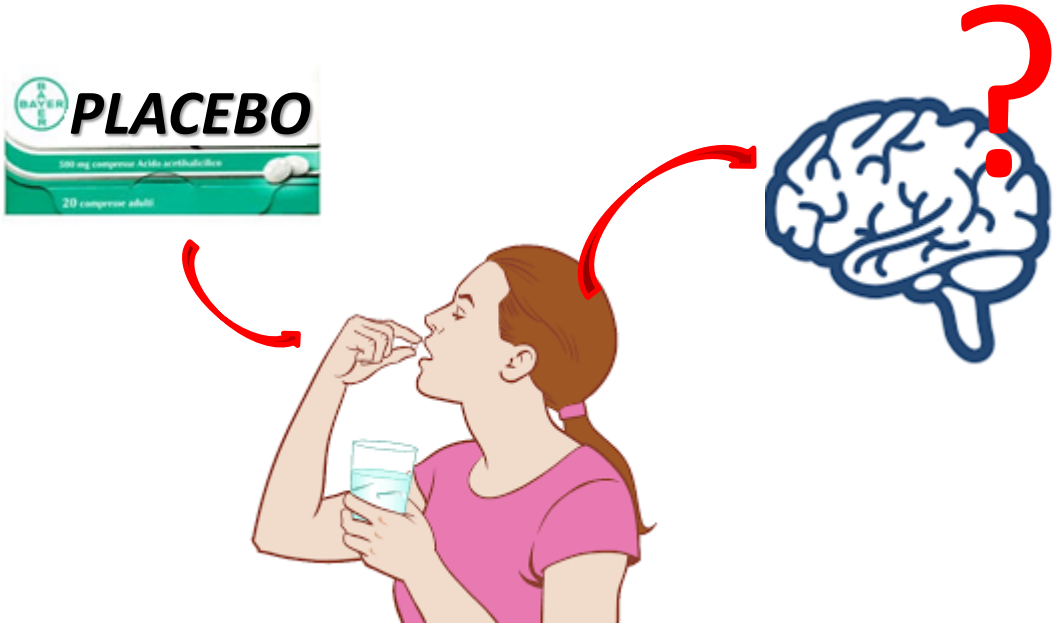
- Decrease of motor output
- Increase of fatigue

Motor outcomes:



Under what conditions does it work?

- Pain
- Motor performance
- Parkinson's disease
- Alzheimer's disease
- Cardiovascular system
- Respiratory system
- Gastrointestinal System
- Immune system
- Endocrine system
- Depression
- Anxiety



Finniss et al. *Lancet* 2010;375:686-95

IMMUNOSUPPRESSION

The immune system can be influenced by associative learning, similarly to behavioral conditioning.

ACQUISITION

- Participants received a **novel-tasting beverage** paired with the **immunosuppressive drug Cyclosporine A**.
- Cyclosporine A normally reduces interleukins and interferon-gamma levels.
- After administration, in the drug group, a clear **decrease in interleukins and interferon-gamma was observed** compared to baseline.

EVOCATION

- Later, participants were given **only the flavored beverage**, without any drug
- Despite the absence of Cyclosporine A, researchers still observed a **significant reduction** in interleukin and interferon-gamma levels, though smaller than in the drug phase.
- This demonstrated a **conditioned immunosuppressive response**

Goebel et al. (2002) *FASEB J.* 16: 1869-1873.

IMMUNOSUPPRESSION

ACQUISITION

EVOCATION

Cyclosporin A (immunosuppressant: reduction of interleukin-2 and interferon)

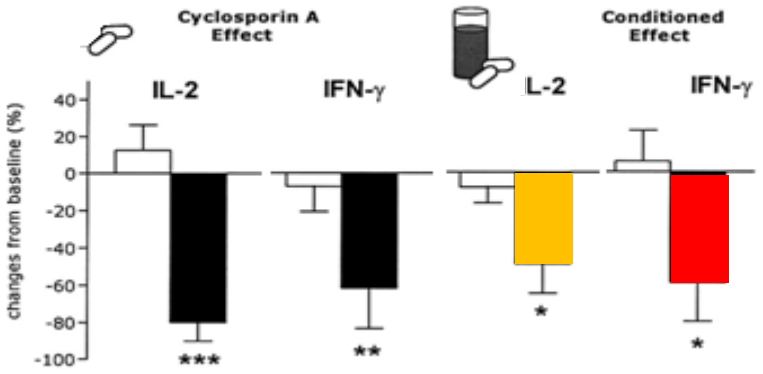
CONDITIONED GROUP

we can produce a placebo effect on hormones and allergic reaction: a placebo can mimic an immunosuppressant drug

Conditioned group

Control group

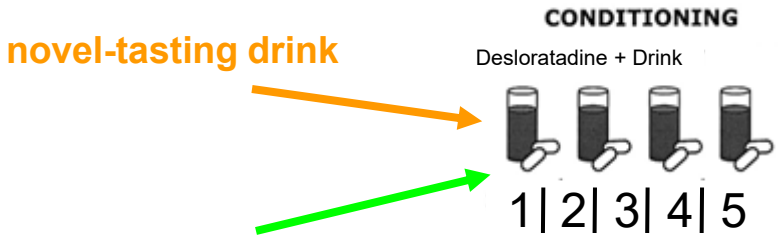
Drug group



Goebel et al. (2002) *FASEB J.* 16: 1869-1873.

ALLERGIC REACTIONS

ACQUISITION



a standard dose of the H_1 receptor antagonist, desloratadine (antihistaminergic drug)→ Basophilic activation reduction

EVOCATION

Water group (water + placebo):

- decreased the **subjective** symptoms
- attenuated the effects of the skin prick test for histamine

Placebo group (novel-tasting drink + placebo):

- decreased the **subjective** symptoms
- attenuated the effects of the skin prick test for histamine
- Reduced basophil activation

Drug group (water + real drug):

= placebo group

Goebel et al. (2008) *Psychother Psychosom 77(4): 227-34.*

HORMONAL CHANGES

- Plasma GH concentration
- Expectancy does not vary GH concentration
- Placebo mimics the effect of sumatriptan (> GH)

	Day 1	Day 2	Day 3
Group 1	No treatment	No treatment	No treatment
Group 2	Suggestion of GH increase	—	—
Group 3	Suggestion of GH decrease	—	—
Group 4	Sumatriptan	Sumatriptan	Suggestion of GH increase
Group 5	Sumatriptan	Sumatriptan	Suggestion of GH decrease

Benedetti et al., 2003

HORMONAL CHANGES

- Plasma cortisol concentration
- Expectancy does not vary cortisol concentration
- Placebo mimics the effect of sumatriptan (< cortisol)

	Day 1	Day 2	Day 3
Group 6	Suggestion of cortisol decrease	—	—
Group 7	Suggestion of cortisol increase	—	—
Group 8	Sumatriptan	Sumatriptan	Suggestion of cortisol decrease
Group 9	Sumatriptan	Sumatriptan	Suggestion of cortisol increase

Benedetti et al., 2003

Under what conditions does it work?

- Pain
- Motor performance
- Parkinson's disease
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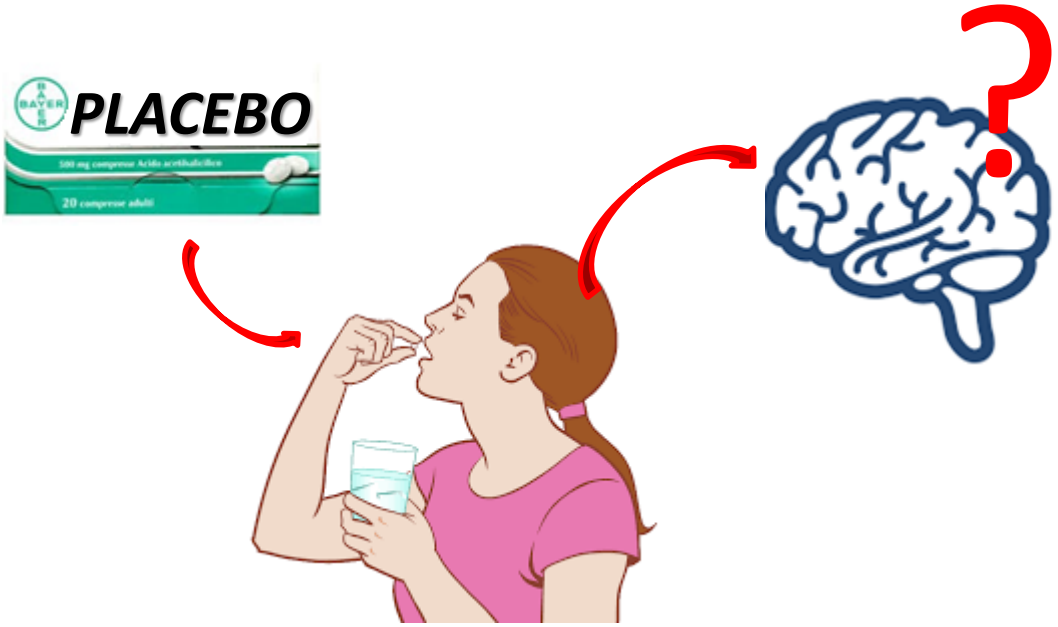
- Gastrointestinal System
- Immune system
- Endocrine system
- Depression
- Anxiety



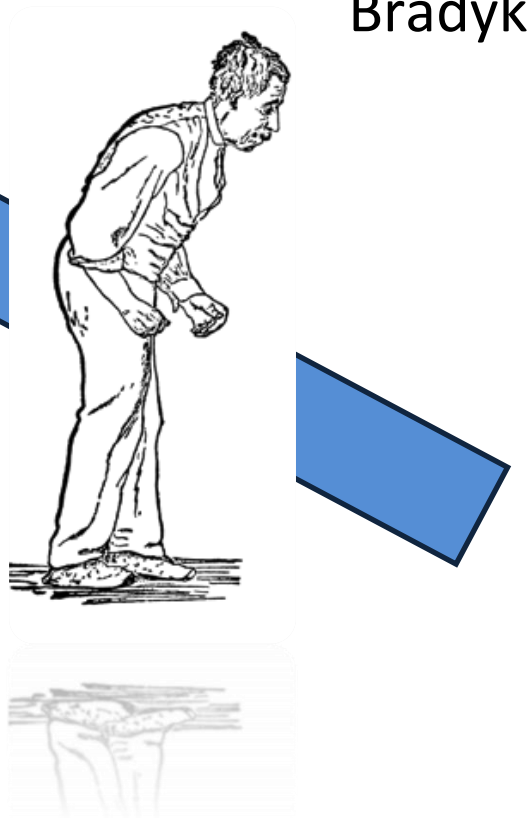
Finniss et al. *Lancet* 2010;375:686-95

Parkinson's Disease (PD)

Freezing

Bradykinesia

Tremor at rest



Rigidity

Postural instability

Symptoms due to **dopaminergic impairment at the level of the substance nigra and striatum** (putamen and caudate):

- From initial **nigrostriatal degeneration**
- Possible **degeneration of several dopaminergic circuits** (mesocortical, mesolimbic tuberoinfundibular)

PD Treatments

- **Drug treatment: L-Dopa**

Levodopa, a **dopamine precursor**, is converted into dopamine by the enzyme **dopa-decarboxylase** in dopaminergic neurons. The main problem is that **only a small fraction (~5–10%) actually reaches the target neurons** in the brain that control motor symptoms. The rest is converted into dopamine elsewhere, where it is not needed, causing **side effects** such as nausea, low blood pressure, heart issues, and involuntary movements.

To reduce these side effects, levodopa is often combined with **peripheral dopa-decarboxylase inhibitors** (like carbidopa or benserazide), which block dopamine formation outside the brain and increase the amount reaching the neurons.

- **Surgical Treatment: DBS**

Deep Brain Stimulation (DBS) is a major surgical treatment for Parkinson's. The patient is awake, with the head fixed, while two microelectrodes are inserted through small holes to stimulate the **subthalamic nucleus**, a key area involved in the disease. Being awake allows doctors to check in real time if the electrodes cause any problems.

Placebo effect and PD

- Clinical trials
- Behavioral Studies
- Neuroimaging studies
  - PET
  - Single neuron recordings
  - EEG

Improvements in RCTs

- Improvement in parkinsonian symptoms in the placebo group in several clinical trials (pharmacological and surgigical)

Goetz et al., (2002, 2008)

- **Pharmacological**: placebo vs sarizotan comparison (serotonergic action) on dyskinesias (involuntary movements)
- **Surgical:** Comparison of patients undergoing real or simulated intra-striatal transplants of pig fetal ventral mesencephalic tissue

As with pain, in many trials the natural history group is missing: the improvement can be due to both the placebo effect and other factors (regression to the mean, spontaneous remission, etc.)

Example of surgical trial

- Surgical trial (McRae et al., 2004):
- No difference between real intervention and placebo ("effectiveness of transplantation of human embryonic dopamine neurons")
- Difference based on **patient perception:**
  - **Patients who thought they had undergone the real surgery had a benefit up to 12 months after the surgery**

- In certain clinical trials, such as those testing **surgical treatments like embryonic dopaminergic neuron transplants**, the observed improvement often came **from the patient's belief that they were in the treatment group**, rather than the treatment itself.
- There was no real difference between the surgical trial and control groups.
- The clinical benefit typically lasted about a year.

This shows that **perception of allocation strongly influences outcomes**.

Even when blinding is properly maintained, patients may form opinions about their treatment, which can affect the measured efficacy.

Improvement in behavioral studies

- The expectation of clinical improvement plays a crucial role
- Typical experimental situation: placebo is administered giving the patient positive expectations of improvement
- **Bradykinesia** is the symptom more sensitive to positive expectations, compared to tremor and stiffness

Improvement in behavioral studies

Patients were divided into two **verbal suggestion groups**:

- **"Bad" condition:** told they would perform poorly
- **"Good" condition:** told they would perform well

They were also told that **DBS would not affect their performance**.

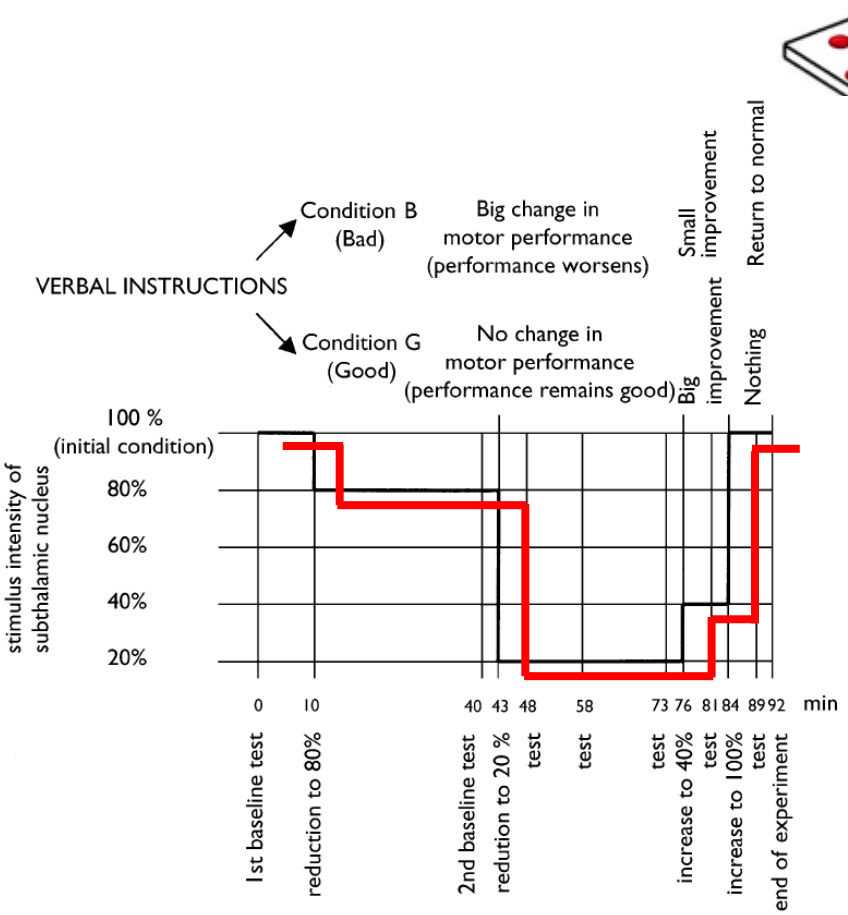
Results showed that **verbal instructions alone could worsen or improve motor performance**.

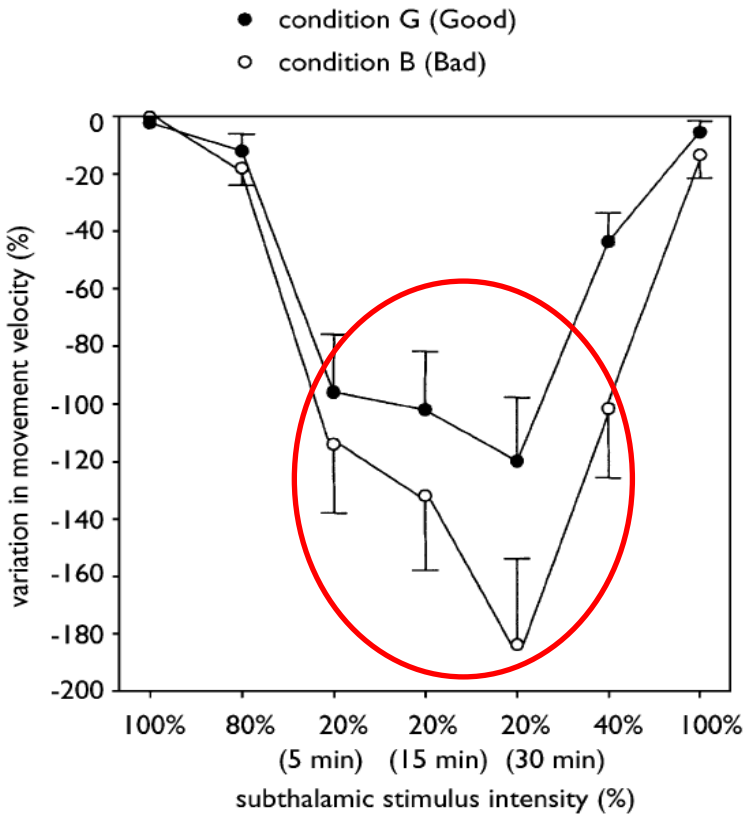
The study also tested **conditioning effects**: if patients were conditioned, their movement speed improved even when later given a **placebo instead of apomorphine**.

This shows that **conditioned placebo effects are stronger and longer-lasting than simple expectation alone**.

Pollo et al., 2002; Benedetti et al., 2003

Improvement in behavioral studies





Pollo et al., 2002; Benedetti et al., 2003

Improvement in PET studies

- First PET study using raclopride
- Raclopride: radiotracer that binds to D2 and D3, competing with endogenous dopamine
- PD patients: knew they could receive placebo or apomorphine

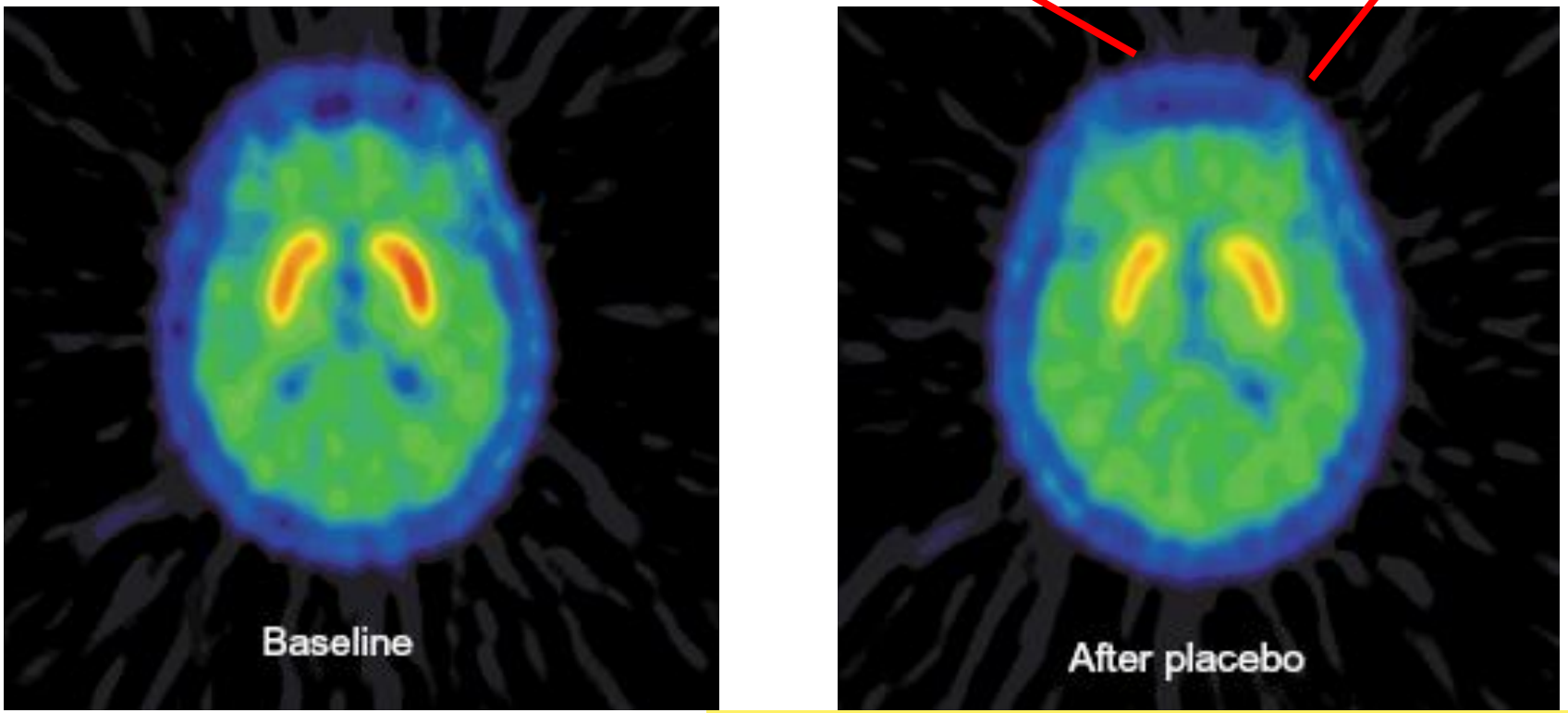
De la Fuente-Fernandez et al. *Science 2001*

Improvement in PET studies

Raclopride binds normally, highlighting dopaminergic sites.

Release of endogenous dopamine at the level of the striatum in PD.

200% increase in dopamine = One dose of amphetamine



Raclopride binding decreased because **endogenous dopamine increased**, showing that **placebo induced dopamine release in the striatum**

De la Fuente-Fernandez et al. *Science 2001*

Improvement in PET studies

- All patients showed a dopamine release BUT only half also reported clinical improvement

- **These patients (clinically improved):** increased release of dopamine at the level of the dorsal striatum.

De la Fuente-Fernandez et al. ***Science 2001***

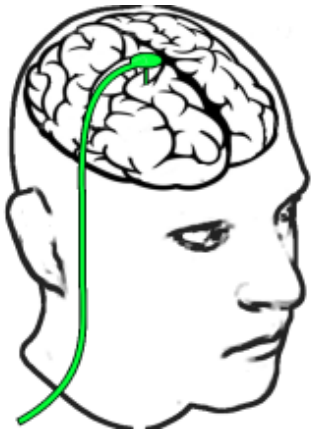
Improvement in PET studies

- Clinical improvement associated with → dorsal striatum (caudate and putamen)
- Expectation of beneficial associated with→ ventral striatum (accumbens)

remember the difference in activation

Improvements in single-neuron studies

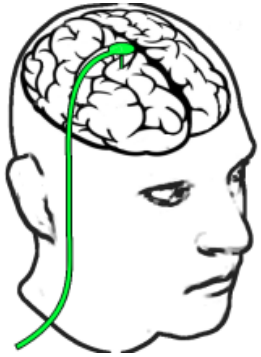
- Double-blind study
- During DBS surgery



- Placebo administered in the operating room after several days of preconditioning with apomorphine

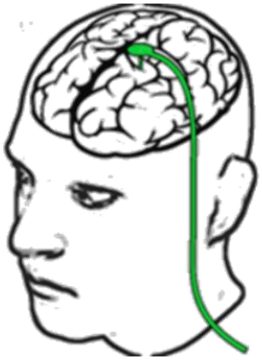
Benedetti, ***Nature Neurosci 2004***

Improvements in single-neuron studies



Basal Recording
of the subthalamic nucleus

placebo

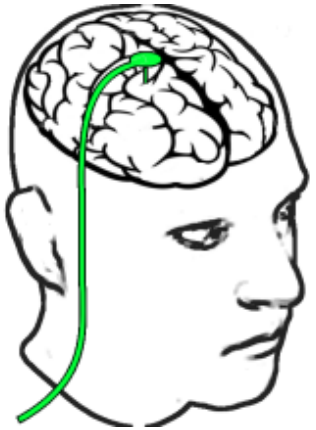


Experimental registration
of the subthalamic nucleus

PLACEBO EFFECT

- **Reduction of wrist rigidity** between pre- and post-treatment
- **Increase in the firing rate of the thalamus** (in the inhibitory circuit of the basal ganglia: the thalamus inhibits the firing rate of the substantia nigra, preventing excessive activity in the subthalamic nucleus and thus avoiding symptoms)
- Reduction in the firing rate of the subthalamic nucleus
- Reduction in the firing rate of the substantia nigra

Improvements in single-neuron studies



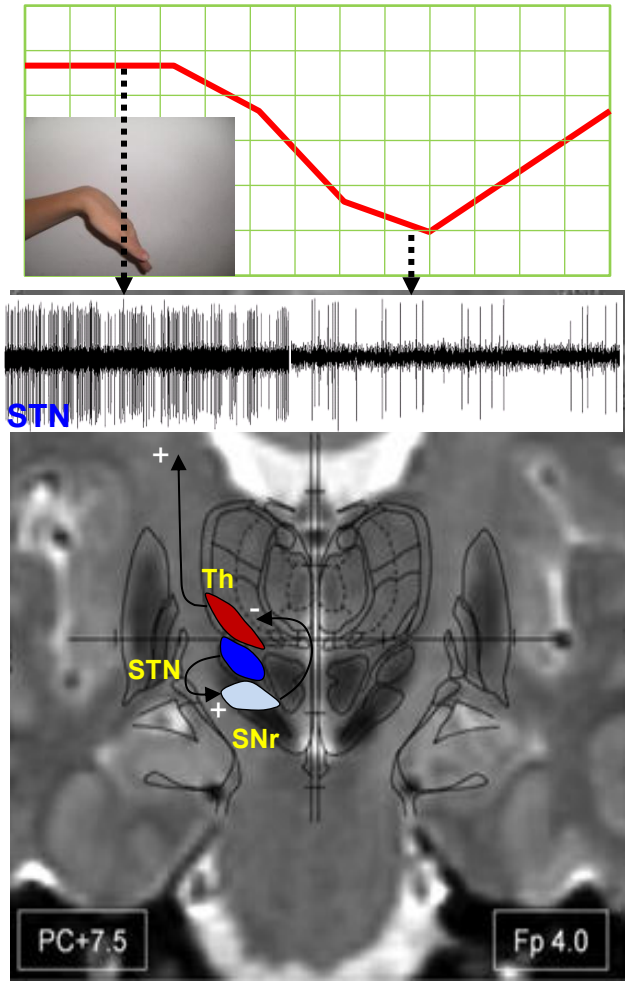
- Extension of previous study
- During DBS surgery

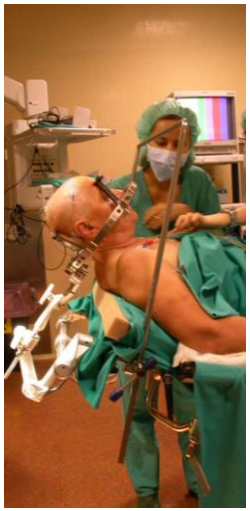
- Analysis of thalamic nuclei (VA, anterior ventral and anterior ventral lateral VLA) and substance nigra

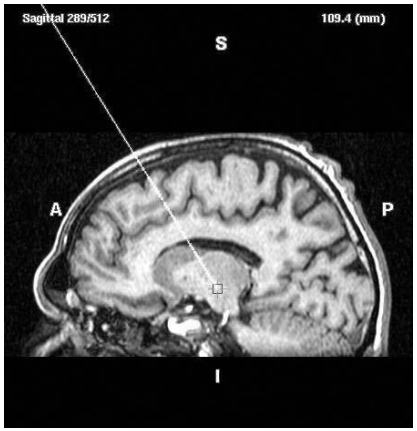
Benedetti, ***J Physiol 2009***

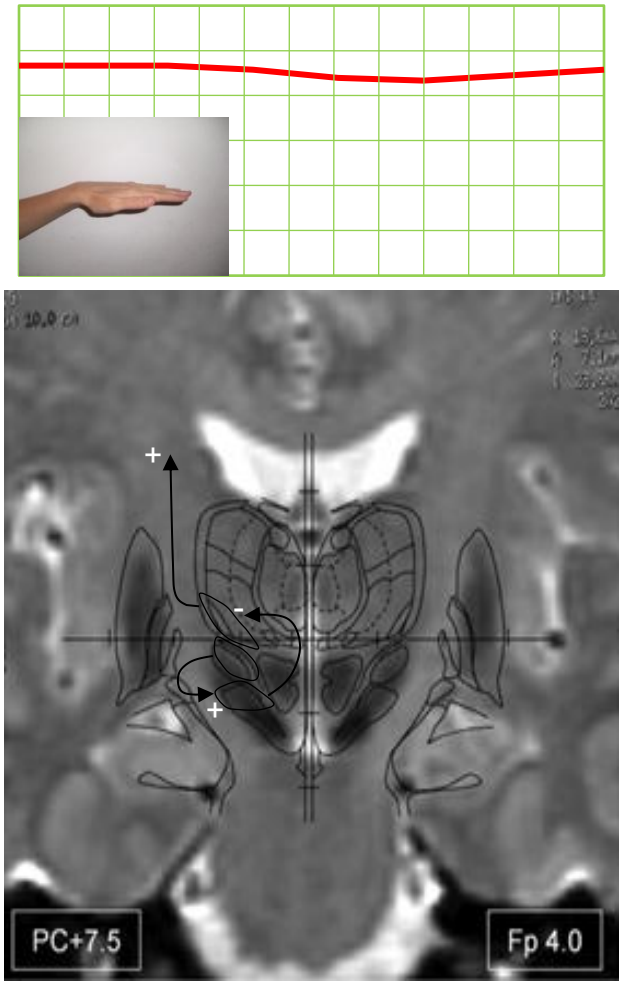
Placebo responder: reduction of firing rate in the STN associated with reduction in the substance nigra and increase in the thalamic nuclei

Placebo non-responder









decrease *increase*

$$\frac{\textit{pre} - \textit{post}}{\textit{pre}}$$ *Neuronal firing rate (Hz)*

Improvements in single-neuron studies

- N = 42 PD patients (DBS)
- 6 experimental groups
- OUTCOMES:
  - Single Neuron Recording (Thalamus)

  - Wrist rigidity

Benedetti et al., *J Physiol, 2016*

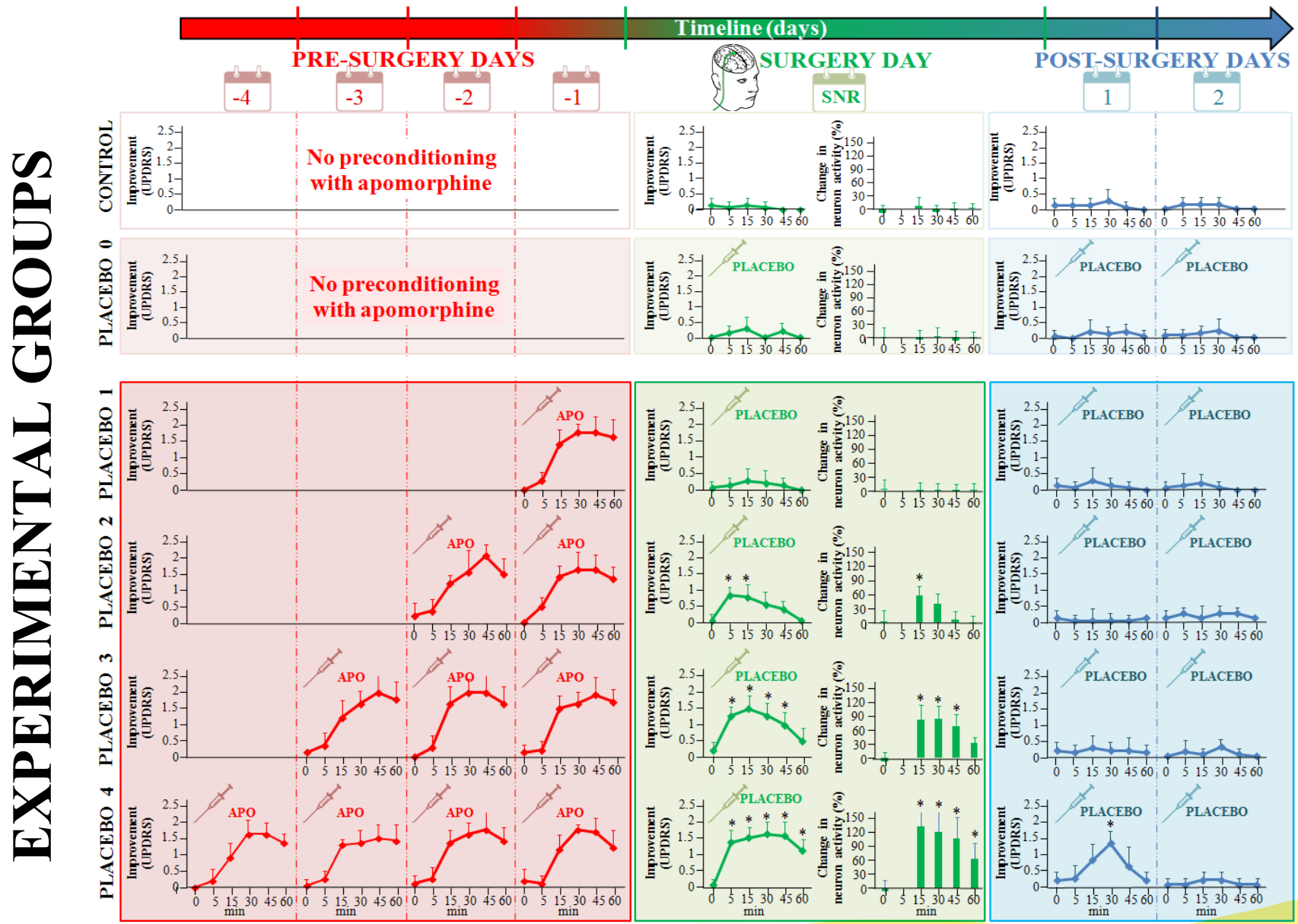
This study showed that **thalamic activity changes** observed during surgery persisted into the next day and depended on **how many apomorphine preconditioning sessions** patients had received.

- **Control group:** no intervention or placebo → no changes in thalamic activity or rigidity.

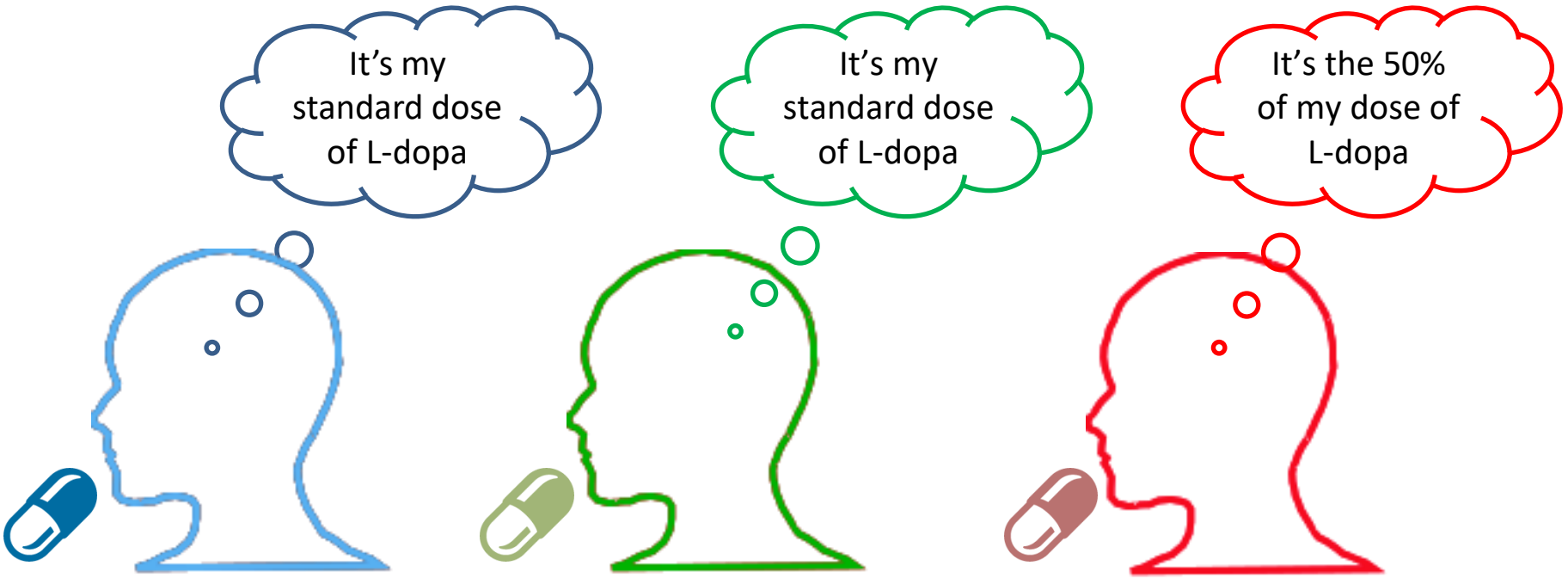
- **Placebo 0:** only expectation of treatment, no preconditioning → no significant effects.

- **Placebo 1–4:** received 1–4 apomorphine preconditioning sessions → the more sessions, the greater the clinical improvement.
- **Placebo 1**: minimal, non-significant effect
- **Placebo 2:** noticeable improvement
- **Placebo 3**: clear improvement in rigidity and thalamic firing
- **Placebo 4**: strong, rapid effect similar to apomorphine

When placebo was administered during surgery, **rigidity improved and thalamic firing rate increased markedly**, lasting up to a day
→The **degree of conditioning directly determined the strength and duration** of the placebo effect.


EXPERIMENTAL GROUPS
Timeline (days)
PRE-SURGERY DAYS
SURGERY DAY
POST-SURGERY DAYS
-4
-3
-2
-1
SNR
1
2
CONTROL
PLACEBO 0
PLACEBO 1
PLACEBO 2
PLACEBO 3
PLACEBO 4
No preconditioning with apomorphine
No preconditioning with apomorphine
Improvement (UPDRS)
Change in neuron activity (%)
APO
PLACEBO
min

EEG STUDY



FULL
= FULL DOSE

DECEIVE
= HALF DOSE

HALF
= HALF DOSE

Carlino et al., Parkinsonisms, 2019

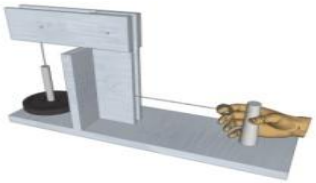
EEG STUDY

1. Full group (get full dose, told full dose)
2. Half group (get half dose, told half dose)
3. Deceit group (get half dose, told full dose)

Medication-off condition

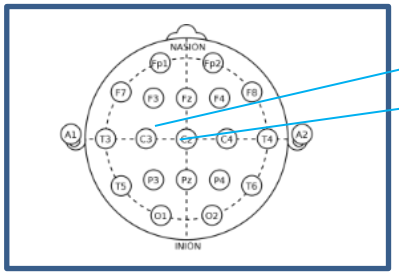
Medication-on condition

UPDRS



Number of flexions

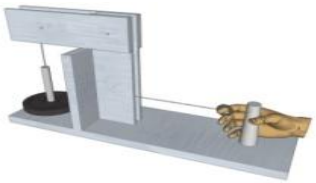
Rate of perceived exertion



Readiness Potential

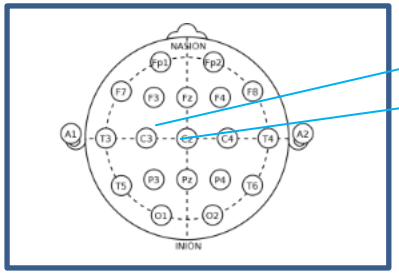
EEG recording

UPDRS



Number of flexions

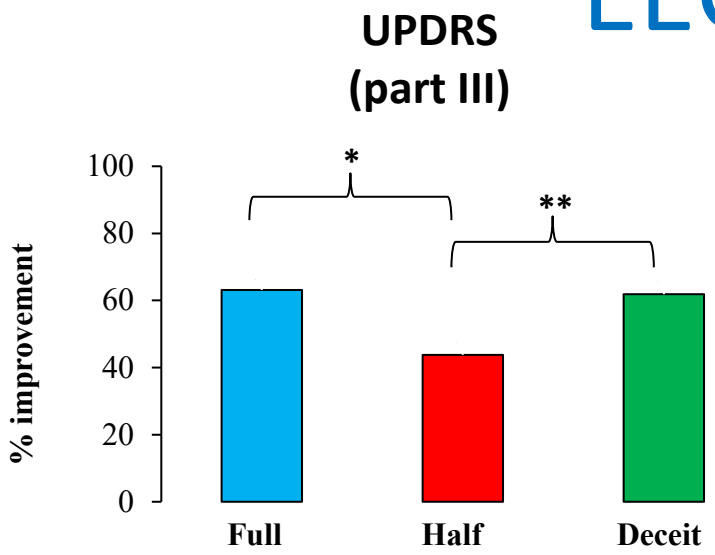
Rate of perceived exertion

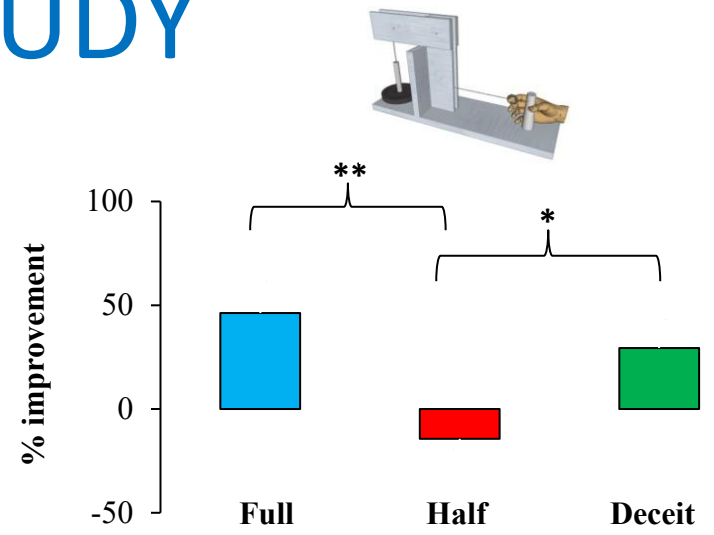


Readiness Potential

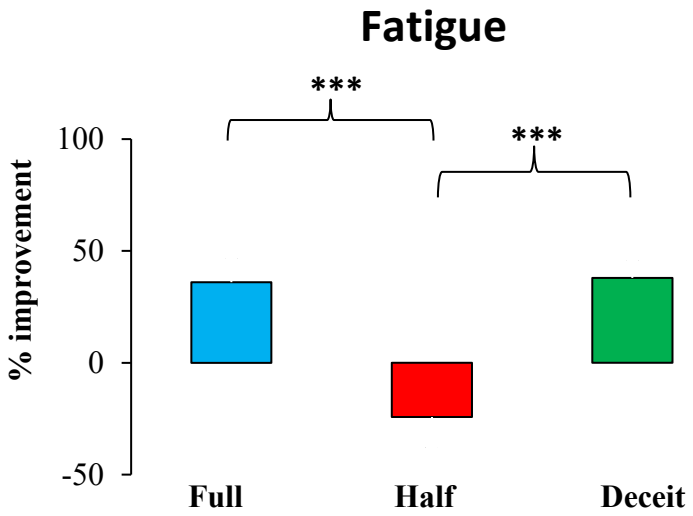
EEG recording

EEG STUDY





Results showed a **large difference** between the two half-dose groups: those who *believed* they received the full dose showed **much greater clinical improvement** than those who knew the dose was reduced.



Conclusion

Patients' **expectations about treatment** can significantly enhance its **clinical efficacy**, even when the actual dose is lower.